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THE FIELD PRODUCTION OF WATER FOR INJECTION

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The requirement exists within the field Army for on-site production of United States Pharmacopeia water for injection (USP WFI) from a potable water source. Research has demonstrated that reverse osmosis (RO) alone is capable of producing non-pyrogenic water but cannot be relied upon to produce USP WFI without pretreatment. Chloride ion, e.g., is not adequately rejected, even with relatively tight membranes. Furthermore, RO membranes are subject to

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20. Abstract (continued)

fouling unless provided high quality feed water; most are damaged by free available chlorine; and rejection of ammonia, if present, is generally poor. The final configuration, which has been subjected to extended testing at anticipated challenge levels, consists, in sequence, of a 5 μ filter for control of fouling; a bed of granular activated carbon for removal of chlorine and trihalomethanes; a mixed bed ion exchange resin cartridge; and the RO element in double pass configuration. A final 0.2 μ filter provides a last line of defense against microbiological contamination. Keywords: Injections (Medicine); Military medicine;

5-micron

0.2-micron

(top)

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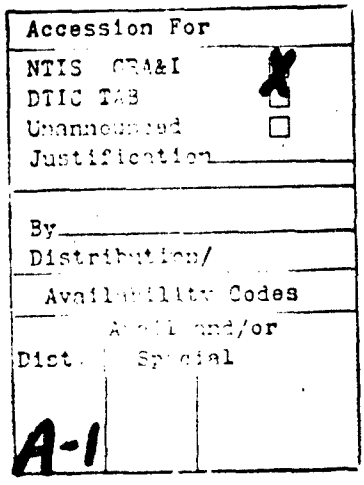

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INTRODUCTION

In consideration of future conflicts, with employment of nuclear, biological, and chemical weapons and the concomitant high potential for casualty generation, field production of non-pyrogenic water for injectables would relieve the logistical burdens associated with resupply. Since a mobile army surgical hospital (MASH) unit assemblage contains 17,534.4 pounds of non-antibiotic injectables and a combat support hospital (CSH) contains 25,404.8 pounds, these stocks may well be utilized within the first few weeks of combat and necessitate resupply.[1]

From historical data, it was found that 154,000 one-liter glass bottles of 0.9 percent sodium chloride were shipped to one theatre of operations in southeast Asia during the period January through December 1969. The gross weight was approximately 681,000 pounds, requiring approximately 25,700 cubic feet of cargo space. The water weight was approximately 336,000 pounds and the glass 342,000 pounds. This resulted in a payload of 49.3 percent of weight in non-pyrogenic water. Had plastic bags rather than glass bottles been utilized, the resulting water weight would have been approximately 88 percent of the total weight.[2] As may be easily ascertained, provisions for considerable volume and weight are necessary to ship non-pyrogenic water for any one solution, whatever the nature of the containers.

If consideration is given to the volume of water contained in the five national stock numbers (NSNs) listed in Table 1 that are in the US Army's medical inventory in a European Theatre of Operations Scenario, then on-site production of non-pyrogenic water may be feasible.

TABLE 1. MEDICAL FLUIDS COMMONLY UTILIZED IN COMBAT HOSPITALS[1]

NSN	Solution
6505 00 083 6537	Ringer's Lactate
6505 00 083 6538	Dextrose 5%, water
6505 00 083 6540	Saline
6505 00 145 0281	Sterile Water
6505 00 543 4048	Sterile Water for Injection

Utilizing the NSNs from Table 1, and coefficients of usage due to casualty generation from the Academy of Health Sciences (Ft. Sam Houston) simulation modeling program, the volumes shown in Table 2 are generated.

TABLE 2. VOLUME OF MEDICAL FLUIDS LISTED IN TABLE 1

Unit Supported	Volume (gal/day)
Division	131.4
Corps (4 Divisions)	8,887.65
*COMMZ (8 Divisions)	8,867.09
Total Theatre (8 Divisions)	23,625.89

*The strength and commitment of COMMZ (Communications Zone) and a Theatre are representative of two entirely different types of organizations. A COMMZ is not committed to fighting, but rather is a training, convalescent, and regrouping area. For example, in World War II, England was the COMMZ for the European Theatre of Operations.

The volume for the total theatre, 23,625.89 gal/day of non-pyrogenic water, translates into 197,032.92 pounds/day (water only) and 3,156.4 cubic feet/day (water only) to be supplied through logistical channels. A detailed calculation for the above is in Appendix A.

As previously mentioned, this consideration was for only five NSNs; water for irrigation was not taken into account. An estimate for water for irrigation is presented in Table 3.[3]

TABLE 3. IRRIGATION WATER VOLUME

	Volume (liters)
Pre Op & Surgery Patients	3.03 L/procedure
Post Op Patient	1.48 L/day
Bedridden Patient	0.75 L/day
Average Diseased Patient	0.50 L/day

(There is no feasible methodology to forecast the number of procedures per patient; for example, one wound, one procedure/patient; two wounds, two procedures/patient, etc.) If an attempt is made to take water for irrigation into account, the figures mentioned in Table 2 will increase dramatically.

If field generation of non-pyrogenic water is an attainable goal, then the alleviation of a major non-combat materiel supply channel would be realized. That is, resupply to the Theatre of Operations from the Continental United States (CONUS) or from the COMMZ would not be burdened by water tonnage or cubage.

The research objective is to delineate a treatment system to produce water for injection (WFI) to meet the standards of the United States Pharmacopeia XX (USPXX). The USPXX standards are reproduced in Appendix B.[4] The input water will be of potable quality. A succession of treatment methodologies will be employed, e.g., turbidity filtration, ion exchange, carbon filtration, and reverse osmosis. The filtration methodologies will be employed prior to the reverse osmosis membrane. This will allow a polished water input to the reverse osmosis membrane, minimizing concentration polarization and increasing the life of the membrane.

REVIEW OF LITERATURE

As stated previously, the input water will be of potable water quality. The following is a review of treatment methodologies for conditioning potable water to meet USPXX WFI requirements. Also, a discussion of the Limulus amebocyte lysate test for pyrogens is included.

ION EXCHANGE

Historical

Since early civilization the Greeks utilized clay and other natural materials for treating water to achieve potability.[5,6] Lord Francis Bacon recognized these materials as being useful to desalinate seawater in his publication The New Atlantis in 1623. Later he presented a methodology for obtaining potable water from seawater in Syla Sylvarum.[5]

In 1756, the Swedish geologist Axel Cronstedt coined the term "zeolite" (from the Greek, zein to boil; lithos, stone) because these natural minerals released water of hydration or combination as steam when boiled.[7,8]

In the 1800's, the English scientist Thompson was credited with recognizing the ion-exchange phenomenon. Another English scientist, Way, continued Thompson's work and made the following observations and conclusions to the Royal Agricultural Society of London:[5]

1. The exchange of calcium and ammonia ions in soils noted by Thompson was verified.

2. Base-exchange substances were silicates, and of the silicates only those that were hydrated displayed any base-exchange properties.

3. Heating soil samples destroyed the base-exchange properties.

4. Base-exchange materials could be synthesized from soluble silicates and alum. Thus, the silicates of aluminum were responsible for the exchange of ions.

5. Exchange of ions is not due to physical adsorption.

6. Some ions are removed more easily then others.

7. Ions are exchanged by equivalent amounts in the soil.

In 1876, Lemberg demonstrated the stoichiometry and reversibility of the mineral leucite ($K_2O Al_2O_3 \cdot 4SiO_2$) by treating with sodium chloride to form analcite ($Na_2O Al_2O_3 \cdot 4SiO_2$). Lemberg could reverse the process by the addition of potassium chloride. This observation led to the use of natural aluminosilicates (zeolites) for water softening.[9]

As with any natural system, a synthetic composition follows. Early synthetic resins were not optimal due to their lack of resistance to abrasion and relatively low molar capacity. In 1935, two English scientists Adams and Holmes observed the ion-exchange capabilities of crushed phenolic phonograph records. This led to the development of synthetic organic ion exchange resins.[9]

Ion Exchanger Compositions

A zeolite has been defined as "an aluminosilicate with a framework structure enclosing cavities occupied by large ions and water molecules, both of which have considerable freedom of movement permitting ion-exchange and reversible dehydration."[7]

To duplicate the ion exchange capabilities of naturally occurring zeolites, synthetic organic resins were most successful. These resins are referred to as either strongly acidic or weakly acidic for cation exchange and strongly basic or weakly basic for anion exchange.

The strongly acidic resins contain strongly acidic functional groups, usually sulfonic, while weakly acidic resins generally have carboxyl groups. Likewise, strongly basic functional groups usually contain quaternary ammonium functions, while weakly basic groups are most often amino in nature.[8]

According to Bernatowicz, the strongly acidic ion-exchangers are employed most often for water treatment, since they are capable of splitting salts. The strong base exchangers are utilized almost exclusively in the production of ultra-pure water since the capability is there to remove weakly ionized material, such as carbon dioxide and silica.[10]

Schematic representations of a strongly acidic ion-exchange resin and a strongly basic ion-exchange resin are represented in Figures 1 and 2, respectively.[8]

Equilibria

According to Weber, the equilibrium exchange reaction between ions in solution and ions attached to a matrix is reversible. Therefore, the description of equilibrium is independent of the direction from which it is approached.[9,11-13]

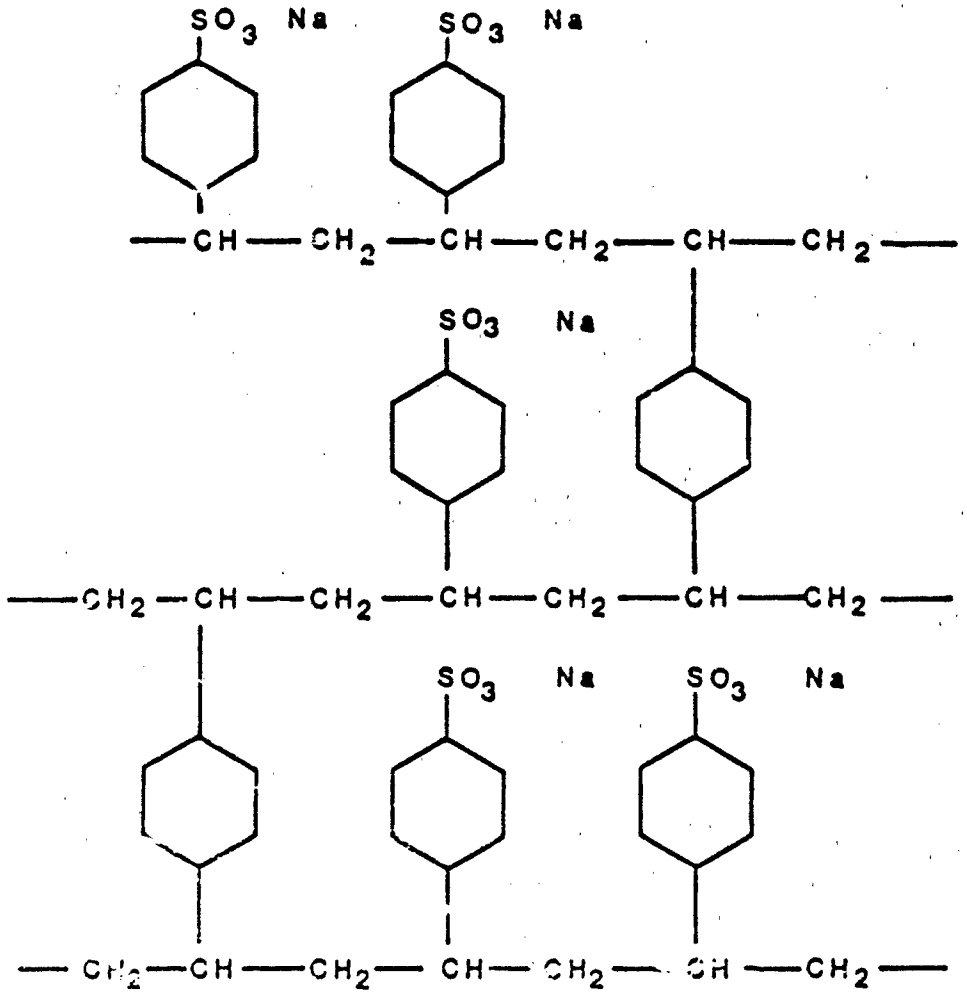


Figure 1. Schematic representation of the three dimensional network of a strongly acidic cation exchanger.[8]

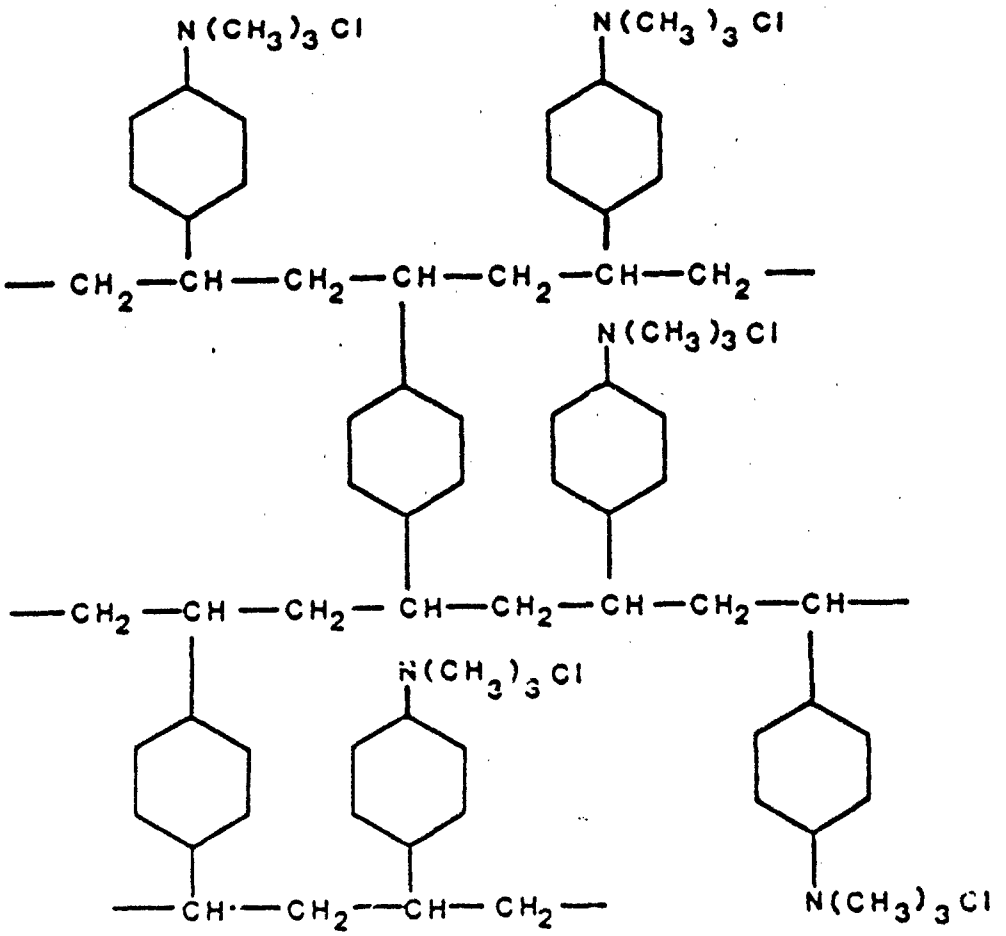


Figure 2. Schematic representation of the three dimensional network of a strongly basic anion exchanger.[8]

If one treats the equilibrium as a chemical reaction, then for cation exchange the following applies:[9]

$$\underset{\text{(solution)}}{A^{n+}} + \underset{\text{(resin)}}{n(R^-)B^+} \;\updownarrow\; \underset{\text{(solution)}}{nB^+} + \underset{\text{(resin)}}{(R^-)_nA^{n+}} \qquad \text{(Equation 1)}$$

Where: (R^-) represents an immobile functional anion group attached to the ion-exchange resin.
A^{n+} is a cation initially in solution
B^+ is a counter-ion initially attached to the resin.

Then according to the law of mass action:

$$K_B^A = (a_B)^n \, (a_{R_nA})/(a_A)(a_{RB})^n \qquad \text{(Equation 2)}$$

where: a_A = activity of ion A in solution
a_B = activity of ion B in solution
a_{RB} = corresponding activities of the ion B in the resin
a_{R_nA} = corresponding activities of the ion A in the resin

K_B^A = selectivity coefficient of ion A over ion B

The K_B^A term is not actually a constant but rather dependent upon experimental conditions.

For dilute solutions, the activity coefficients of the ions in solution approach unity and are therefore replaced by their molal concentrations $[B^+]$ and $[A^{n+}]$. The resin phase cannot be treated as such and must therefore undergo corrections for activity. If $a_i = X_i f_i$, the activities a_{RB} and a_{R_nA} can be replaced by the following:

$$a_{R_nA} = (X_{R_nA})(f_{R_nA}) \qquad \text{(Equation 3)}$$

$$(a_{RB})^n = (X_{RB})^n (f_{RB})^n \qquad \text{(Equation 4)}$$

where: X = the equivalent ionic fraction
f = the activity coefficient

The quantity $[B^+]^n \, (X_{R_nA})/[A^{n+}](X_{RB})^n$ is determined experimentally and is designated K^o, which is the "apparent equilibrium constant." Substituting into the above equation yields:

$$K^o = K_B^A \frac{(f_{RB})^n}{(f_{R_nA})} \qquad \text{(Equation 5)}$$

K^o must not be considered a rigorous constant due to the variability of $(f_{RB})^n/(f_{R_nA})$. However, over narrow concentration ranges, K^o does exhibit some validity. It is most useful in determining which ions will exchange in reasonable amounts, thereby giving an estimate of the quantity of resin required to remove an ion under question.

Gregor stated that K^o is a function of deviation from ideal behavior. To reach his conclusions concerning K^o, Gregor neglected solvent transport and pressure-volume free energy, and assumed that the standard chemical potential of each diffusible species is the same in both resin and solution.[14]

Another concept to explain ion-exchange equilibrium is based on Donnan Theory,[9,12,15] which relates to unequal distribution of ions across a membrane.

Donnan theory states that the product of the activities of the mobile ions of individual salt species on one side of the membrane must equal the product of the activities on the other side.[16]

Substantial concentration differences arise when a dilute solution of a strong electrolyte comes in contact with the resin phase. There is the tendency of concentration gradients to equilibrate by diffusion of ionic species into and out of the resin phase. With ionic species, electroneutrality is at an imbalance as diffusion occurs, so that an electric potential is built up between the resin and solution phases. This difference in potential (the Donnan potential) tends to draw counter-ions back into their respective phases, i.e., cations into a "negatively charged" resin phase and anions into a "positively charged" solution phase. Hence, an equilibrium exists in which the tendency of ionic species to diffuse in response to concentration gradients is balanced by a potential field. The Donnan Theory is a more sophisticated thermodynamic interpretation of ion-exchange phenomena than is the mass action law description. However, the mass action law approach is quite useful if one considers K^o (the "apparent equilibrium constant") constant only over a limited range.[3]

Ion Selectivity

The ion-exchange reaction involves equivalent change; this is shown in Equation 1 and in the resulting selectivity coefficient K_B^A in Equation 2.

The selectivity of a resin for a particular ion is described by the distribution coefficient K_d, which is defined in Equation 6.

$$K_d = \frac{\text{(concentration of ion/unit weight of resin)}}{\text{(concentration of ion/mL of solution)}} \qquad \text{(Equation 6)}$$

Therefore for the exchange reaction between A^{n+} and B^+,

$$K_d^A = \frac{\text{(moles } A^{n+}\text{/g resin)}}{\text{(moles } A^{n+}\text{/mL solution)}} \qquad \text{(Equation 7)}$$

$$K_d^B = \frac{\text{(moles } B^+\text{/gram resin)}}{\text{(moles } B^+\text{/mL solution)}} \qquad \text{(Equation 8)}$$

The ratio of K_d^A/K_d^B is the separation factor or selectivity coefficient Q_s.

$$Q_s = \frac{K_d^A}{K_d^B} = \frac{\text{(moles } A^{n+}\text{/g resin)(moles } B^+\text{/mL solution)}}{\text{(moles } B^+\text{/g resin)(moles } A^{n+}\text{/mL solution)}} \qquad \text{(Equation 9)}$$

and

$$Q_s = \frac{[R_nA][B^+]}{[RB][A^{n+}]} = \frac{(X_{R_nA})[B^+]}{(X_{RB})[A^{n+}]} \qquad \text{(Equation 10)}$$

where: $[R_nA]/[RB]$ is the molar ratio of the ions A^{n+} and B^+ in the resin in equilibrium with the molar concentrations $[A^{n+}]$ and $[B^+]$ in the solution.

X_{R_nA} is the equivalent ionic fraction of bound A^{n+}

X_{RB} is the equivalent ionic fraction of bound B^+

The interpretation of Q_s is.

$Q_s = 1$, the resin has no preference for either ion.

$Q_s > 1$, the resin has a preference for ion A over ion B.

$Q_s < 1$, the resin has a preference for ion B over ion A.

The value of Q_s is an important consideration in choosing a resin for a particular requirement. The larger Q_s is, the greater the possibility for a shorter ion-exchange column, a higher flow rate, and better separation.[9]

For a given series of similar ions, there is a general order of affinity for the resin. For most synthetic resins, the typical series of increasing affinities are:[8]

$$Li < H^+ < Na^+ \; K^+ = NH_4^+ < Rb^+ < Ag^+$$

$$Mg^{++} = Zn^{++} < Cu^{++} < Co^+ < Ca^{++} < Sr^{++} < Ba^{++}$$

$$F^- < HCO_3^- < Cl^- < Br^- < NO_3^- < I^- < ClO_4^-$$

Figure 3 represents exchange isotherms for sodium in the presence of calcium in varying concentrations of sodium. As the molar concentration of sodium increases, the resin shows an increase in preference for sodium over calcium. The dotted line represents an isotherm for an exchanger with no selectivity.[8]

General

Ion exchange is useful in several areas, these include:[17]

1. Conversion--Replacement of one ion species for another.

2. Concentration--ions in low concentration are adsorbed onto a resin and eluted off in a concentrated form.

3. Purification and Deionization--This is the complete removal of a species by utilizing the hydrogen form of a cation exchanger and the hydroxide form of an anion-exchanger.

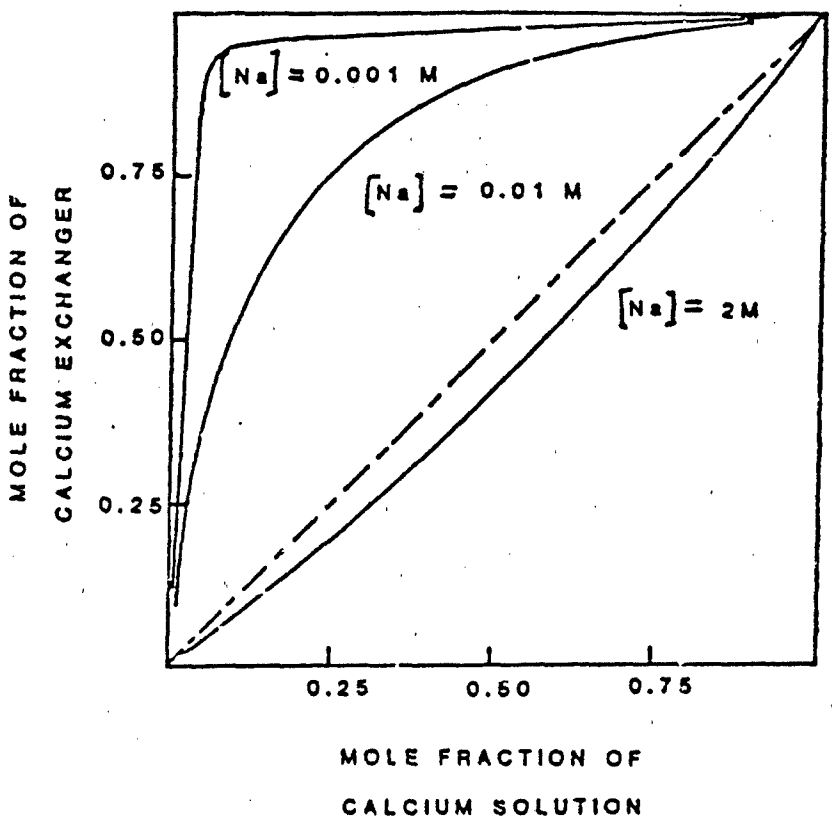


Figure 3. Exchange isotherms for the reaction:

$$Ca^{++} + 2(Na^{+}R^{-}) = (Ca^{++}R_2^{=}) + 2Na^{+}.$$

In dilute solutions the exchanger shows a strong preference for Ca^{++} over Na^{+}. This selectivity decreases with increasing ion concentration. The 45° line represents the isotherm for an exchanger with no selectivity. The exchanger can be regenerated with concentrated salt solutions.[8]

4. Fractionation (ion-exchange chromatography)--Separation of mixtures where minute differences in selectivity exists.

Ion exchange has been utilized to soften water rather than the calcium hydroxide-soda ash method. The reactions described below are those occurring on a cation exchange resin.[5]

$$Ca(HCO_3)_2 + Na_2R \rightarrow CaR + 2NaHCO_3$$

$$Mg(HCO_3)_2 + Na_2R \rightarrow MgR + 2NaHCO_3$$
carbonate hardness

$$CaSO_4 + Na_2R \rightarrow CaR + Na_2SO_4$$

$$CaCl_2 + Na_2R \rightarrow CaR + 2NaCl$$

$$MgSO_4 + Na_2R \rightarrow MgR + Na_2SO_4$$

$$MgCl_2 + Na_2R \rightarrow MgR + 2NaCl$$
noncarbonate hardness

Trace amounts of aluminum will be removed along with small amounts of iron and manganese:

$$Fe(HCO_3)_2 + Na_2R \rightarrow FeR + 2NaHCO_3$$

$$Mn(HCO_3)_2 + Na_2R \rightarrow MnR + 2NaHCO_3$$

$$Al_2(SO_4)_3 + 3Na_2R \rightarrow Al_2R_3 + 3Na_2SO_4$$

The major drawback to repeated use of the resin is the complexing of iron, manganese, and aluminum. Only negligible amounts of these ions are removed during backwashing. Ultimately they accumulate on the resin and affect the exchange capacity.

Another major drawback of water softening with resins is the bacterial slime and organic coatings that accumulate on the resin, thus reducing exchange capability.[5,20]

Ion-exchange is utilized primarily for preparing water for boiler feed as the method of choice,[18] and for high purity water for the electronics industry.[19] For the above uses, Otten suggests that specific resistance is adequate for quality control where one is only interested in ionized solids.[21]

Recently, ion-exchange has been successfully utilized in nitrate removal, while the exchanger clinoptilolite has generated much interest in ammonia removal.[13,22-24] Also, Cox reports on ion-exchange membranes in electrodialysis.[25]

More recently, Chiou et al. reported on a resin that removes nitrate and nitrite along with oxidizing ions from a solution, without pH sensitivity, in the 4-10 range.[26]

CARBON ADSORPTION

Historical

The use of charcoal ("carbon") other than as fuel dates back to the ancient Egyptians. Ingestion of charcoal for medicinal purposes was mentioned in an Egyptian papyrus from 1550 B.C. During the time of Hippocrates, wood chars were again introduced into the medical arena.[27,28]

In 1773, Scheele, experimenting with gases, became aware of the adsorption phenomenon. Lowitz, in 1785, found carbon to be useful in removing impurities from water and subsequently discovered its decolorizing powers. In 1793, Kehl utilized char to remove odors from gangrenous ulcers on patients. Owing to experiments by Figuers in 1811, bone char was found to be more efficient for decolorizing than charcoal; this contributed to the refining processes in the sugar industry. It was not until 1862 that carbon was utilized to render water potable. Interest in adsorption led Ostrejko in 1900 to patent processes for the manufacture of activated carbon. This led to the development of modern commercial activated carbon. Great interest concerning the adsorption powers of activated carbon for personnel protection was expressed in 1915. The use of "toxic gases" in WWI led to the development of granular carbon, as powdered carbon was not suitable for gas masks.[9,28,29]

Manufacture of Carbon

The term "activated charcoal" designates a group of carbonaceous solid absorbents prepared from different materials such as: wood, bone, petroleum residues, and coal. Each commercial producer has proprietary processes; therefore, many types of "carbon" exist; these differ with respect to pore size and surface area.[30]

The following is a general outline of processing steps for the manufacture of activated carbon.

The first step is carbonization, which is the formation of a char from a source material. This is accomplished by heating (usually in the absence of air) to a high enough temperature to dry and volatilize substances in the carbon. Dehydrating salts, such as calcium chloride, magnesium chloride, and zinc chloride are used to catalyze the carbonization process. The ratio of salt to raw material is important in that it affects certain characteristics manifested during carbonization. The chars produced by this step have relatively little internal surface area for adsorption.

The increase in surface area is accomplished through "activation" by oxidizing agents such as steam, air, or carbon dioxide at elevated temperatures. The oxidizing gases attack the more readily oxidizable portions of the char, thus producing a porous structure with an extensive internal surface. The activation by oxidation depends upon the following parameters:[30,31]

1. The oxidizing gas and its concentration,
2. The temperature during oxidation,
3. The extent to which the activation is conducted,

4. The raw materials contained within the char, and
5. The amount and nature of the inorganic additives during oxidation.

Typically, the surface areas available in activated carbon range from 500-1400 m^2/g.[9]

Adsorption

Adsorption involves the interphase accumulation or concentration of substances at a surface or interface. The process can occur at an interface between two phases, such as liquid-liquid, gas-liquid, gas-solid, or liquid-solid interphases. The material being adsorbed is the adsorbate and the adsorbing material is the adsorbent.[12]

The graphical illustration in Figure 4 represents the differences among favorable adsorption, linear adsorption, and unfavorable adsorption. The abscissa denotes the concentration of the migrating substance in the liquid phase in contact with the solid phase at a liquid-solid interface. The ordinate denotes that amount of substance that has moved across the interface. Curves I and III represent a curvilinear dependence upon the amount concentrated at the solid surface for both favorable and unfavorable adsorption, respectfully. Curve II indicates a linear pattern which occurs in direct proportion to concentration.[9]

The explanation of adsorption is usually in terms of surface tension or energy per unit area. That is, molecules in the interior of the solid phase are subjected to equal forces in all directions while molecules at the surface are subject to unbalanced forces, thus other molecules become attached to the surface. This type of adsorption is known as physical adsorption or physisorption. Physical adsorption is due primarily to weak attractive forces or Van der Waals forces. Physisorption allows the adsorbate to become multilayered.[28,32,33]

In direct contrast to the physisorption, which is a reversible phenomenon, is chemical adsorption or chemisorption. Chemisorption entails a chemical reaction between the adsorbate and the adsorbent. Because a chemical reaction occurs, the phenomenon of chemisorption is considered irreversible as opposed to physisorption. During chemisorption, equilibrium is obtained once the concentration of the contaminant in solution is in dynamic balance with that at the surface of the adsorbent. During chemisorption, essentially a new compound is formed due to the reaction between the absorbate and absorbent. Unlike physisorption, chemisorption produces a layer one molecule in depth, as opposed to several molecules in depth.[7,32,33]

As with any physicochemical system, numerous parameters may affect the adsorption phenomenon. Kirk et al. divided the properties affecting adsorption into physical and chemical. Under the term "physical," the most important property is surface area. The available area depends upon the molecular size of the adsorbate and the pore diameter of the adsorbent. Activated carbons utilized in contact with the liquid phase have pore sizes of 3 μm and larger. This is to accelerate the diffusion of the potential adsorbate in solution into the pores. As to the molecular dimensions of the

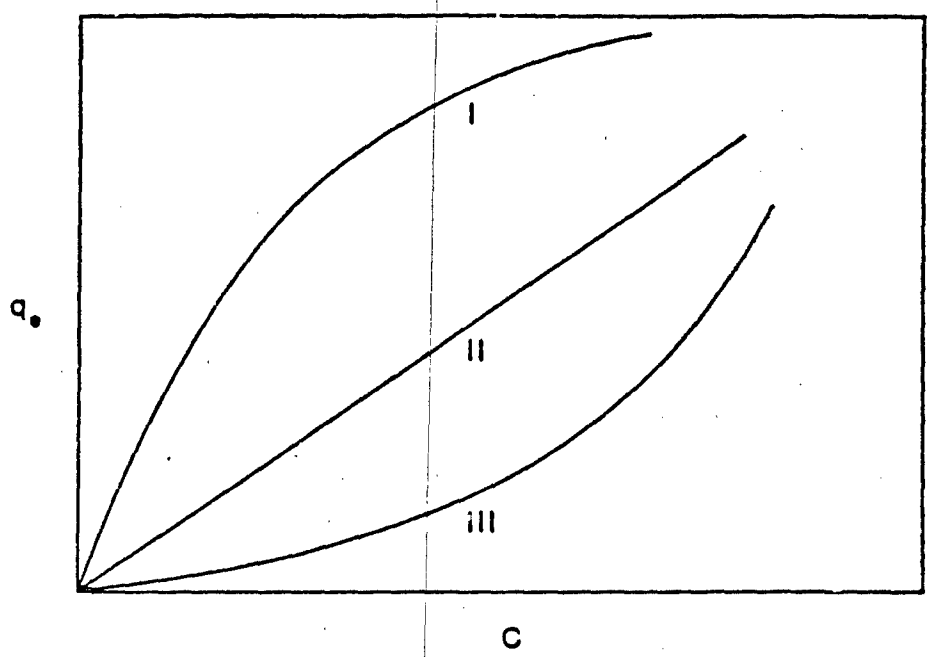


Figure 4. Types of Adsorption. C = the concentration of the migrating substance in the liquid phase in contact with the solid phase at a liquid-solid interface. The q_e term denotes that amount of the substance that has moved across the interface. Curves: I Favorable Adsorption; II Linear Adsorption and Absorption; III Unfavorable Adsorption.[9]

adsorbate, Kirk states that adsorption varies inversely with molecular size, i.e., the smaller the particle the faster the adsorption rate.[23,34]

The chemical properties of the carbon affecting adsorption are primarily ash content, ash composition, and pH. According to Kirk et al., discrepancies between expected performance of an activated carbon based on surface area and pore size distribution data and actual adsorption capacity may often be explained by oxygen-containing groups on the surfaces of the carbon.[33] The pH is a measure of surface acidity or basicity of these groups, and aids in predicting hydrophilicity and anionic or cationic adsorption preferences of the carbon.[28,29,34-36]

The presence or absence of a charge (ionization) on a molecule affects adsorbability. Hassler states that a solution of aniline and phenol (equimolar) shows the following adsorption preference as a function of pH:[30]

pH 7--both molecules equally adsorbed
pH 10--aniline is preferentially adsorbed (since phenol is ionized)
pH 3--phenol is preferentially adsorbed (since aniline is ionized)

Morris and Weber found that temperature affects the kinetics of adsorption of alkylbenzenesulfonates; an increase in temperature increases the rate. The authors concluded that adsorption is controlled by intraparticle diffusion. The equation employed by Morris and Weber to decribe the temperature effect is the familiar:[34]

$$k = Ae^{-E/RT} \qquad \text{(Equation 11)}$$

where: k = the specific rate constant
A = frequency factor (temperature independent)
E = activation energy (the minimum energy the system needs for the reaction to occur)
R = universal gas constant
T = absolute temperature

According to Ekenfelder, the adsorption of typical organic pollutants from water generally increases with decreasing pH and the extent of adsorption (in contrast to the rate) increases with decreasing temperatures.[31]

Cookson identified functional groups on the surface of activated carbon; of these the phenolic, carboxylic, and lactone are considered as acidic surface oxides. Cookson[30] listed the functional groups as (see Figure 5):

1. Carboxyl
2. Phenolic hydroxyl
3. Quinone type carboxyl
4. Normal lactones
5. Fluorescein type lactones
6. Carboxylic acid anhydrides
7. Cyclic peroxide

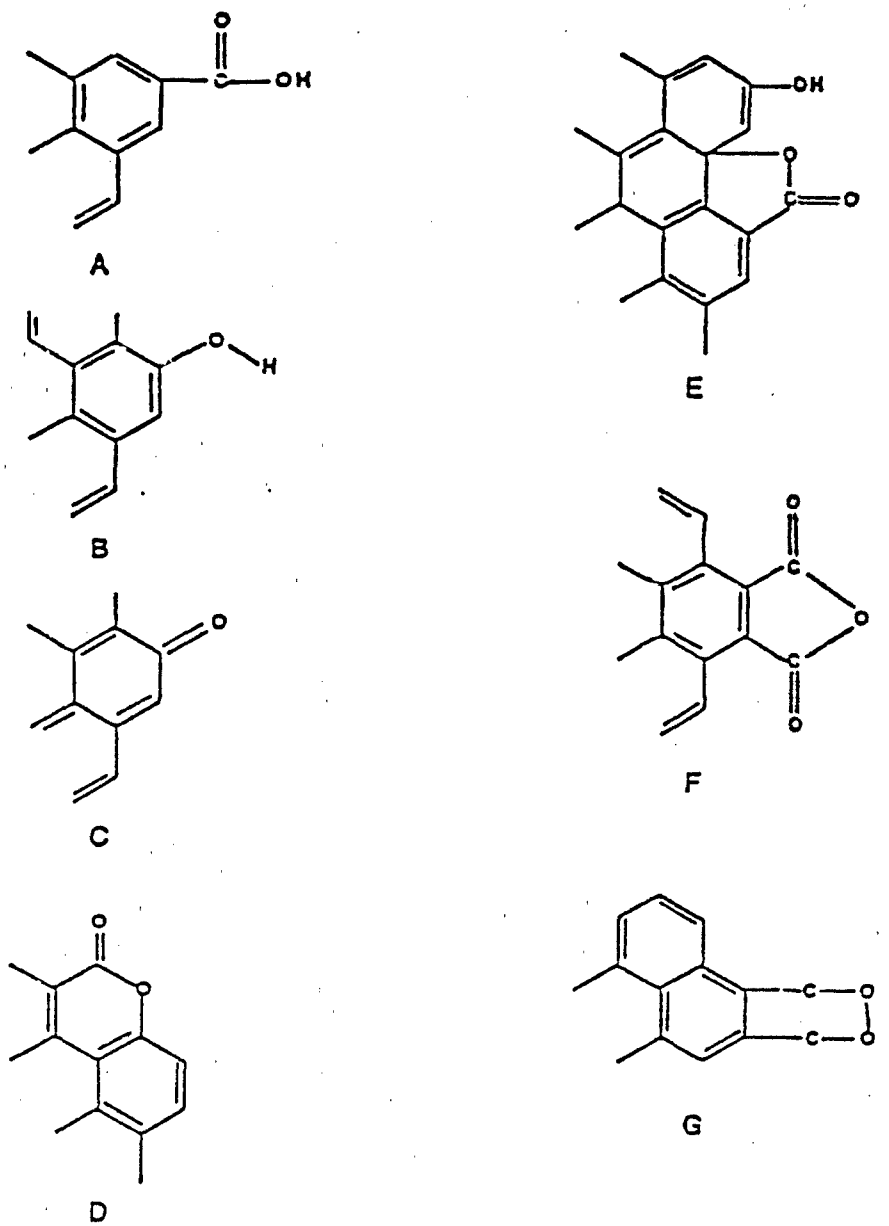


Figure 5. Functional groups on the surface of activated carbon: A - Carboxyl, B - Phenolic hydroxyl, C - Quinone type carboxyl, D - Normal lactone, E - Fluorescein type lactone, F - Carboxylic acid anhydride, G - Cyclic peroxide.[30]

An assortment of factors affecting adsorption has been presented:[30]

1. Influence of Molecular Structure on Adsorbability:

a. Aromatic compounds are generally more adsorbable than are aliphatic compounds of similar molecular size.

b. Branched-chain aliphatic compounds are more adsorbable than their straight-chain analogs.

c. The position of substitution in an aromatic compound (-ortho, -meta, -para) modifies adsorption.

d. Stereoisomers show inconsistent patterns.

e. Optical isomers (dextro- and levo-) appear to be equally adsorbed.

2. Solubility--An increase in solubility reflects a greater affinity between the solvent and the solute. This affinity acts to oppose the attraction to the carbon surface. Thus, introduction of polar (more hydrophilic) groups leads to diminished adsorption from an aqueous solution.

3. Ionization--Usually ionization adversely affects carbon adsorption. Undissociated molecules of organic compounds are more readily adsorbed than are ions of dissociated molecules. Hence, low pH will favor adsorption of organic acids and a high pH favors adsorption of organic bases.

4. Multiple Solutes--Different species compete for the same adsorptive site. Therefore, adsorption of each compound is less than from a single-solute solution. Also, some solutes alter the solution status of other specific solutes. Potassium iodide increases the solubility of iodine by forming I_3^- and thereby decreases the amount of iodine adsorbed.

5. Co-Adsorption--Some solutes are able to enhance the adsorption of other specific solutes. For example, cholesterol and saponin mutually increase each other's adsorption.

6. Solvent influence--The liquid medium greatly influences the adsorbability of solutes. Organic solutes adsorb well from water but not from organic solvents.

7. Temperature--Except when a chemical reaction occurs (chemisorption), elevation in temperature diminishes adsorption by increasing the escaping tendency of a vapor or gas within the interstices of the activated carbon.

Isotherms

Hassler has stated that although isotherms are extremely useful in any serious adsorption study, the availability of isotherms is not essential to the successful use of activated carbon in any new application.[27]

Of the isotherms utilized in evaluating activated carbon, the Freundlich equation, which is essentially empirical, is used mainly for comparison of powdered carbons. Since powdered carbons are not applicable to this study, the review of isotherms will be directed at the Langmuir, and the Brunauer-Emmett-Teller (BET) models.

1. Langmuir isotherm:[7,30]

   a. The adsorption is limited to a monomolecular layer,

   b. The surface of the activated carbon is energetically homogeneous,

   c. There is no interaction between the adsorbed molecules.

Graphically, the Langmuir isotherm has the curvilinear form shown in Figure 6.

According to Eckenfelder, both the rate and the adsorption capacity will increase with increasing concentration of solute in solutions, and also conversely. This would imply that with respect to organics, the Langmuir isotherm is based on an equilibrium between condensation and evaporation of adsorbed molecules.[31]

The Langmuir isotherm is expressed as:

$$X/M = \frac{a\ b\ C}{1 + aC} \qquad \text{(Equation 12)}$$

where: X = weight of the substance adsorbed
M = weight of the adsorbent
C = equilibrium concentration of contaminant
a = pore radius
b = Langmuir constants related to adsorption energy.

The most useful form of the Langmuir isotherm is the linearized form:

$$\left(\frac{X}{M}\right)^{-1} = \frac{1}{b} + \frac{1}{ab} \cdot \frac{1}{C} \qquad \text{(Equation 13)}$$

The graphical representation now becomes as in Figure 7.

Fair et al. states that although the Langmuir equation may be used in comparative tests to identify the magnitudes of the pertinent adsorption coefficients of a given adsorbent, the equation is seldom fitted to observed information. Rather, experimental carbon dosage is plotted against observed residual concentrations of the sorbate and the required carbon dosages are read from curves fitted by eye utilizing either arithmetic or log-log plots.[8]

2. Brunauer-Emmett-Teller (BET) isotherm: The BET isotherm was developed by applying Langmuir's concept to multimolecular adsorption.[9,29]

   a. Only the first layer of molecules adsorbed are bound to the surface by adsorption forces orginating from interaction between the adsorbent and the adsorbate,

   b. The forces acting in multimolecular adsorption are the same as those acting in the condensation of vapors,

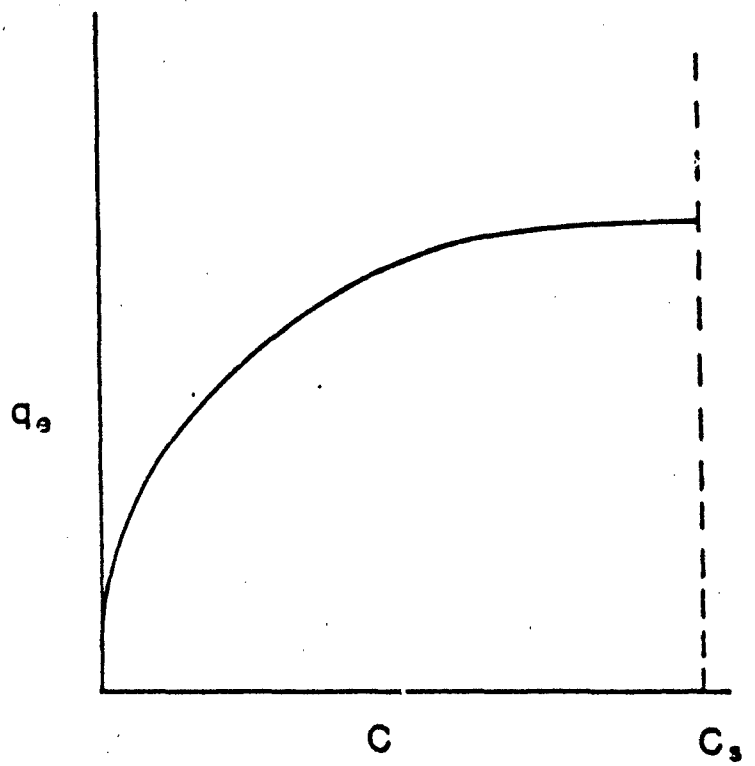


Figure 6. Langmuir isotherm. Where:
q_e = The number of moles of solute adsorbed per unit weight adsorbent at concentration C,
C = The measured concentration of solution at equilibrium,
C_s = The concentration of the solution at saturation.[8]

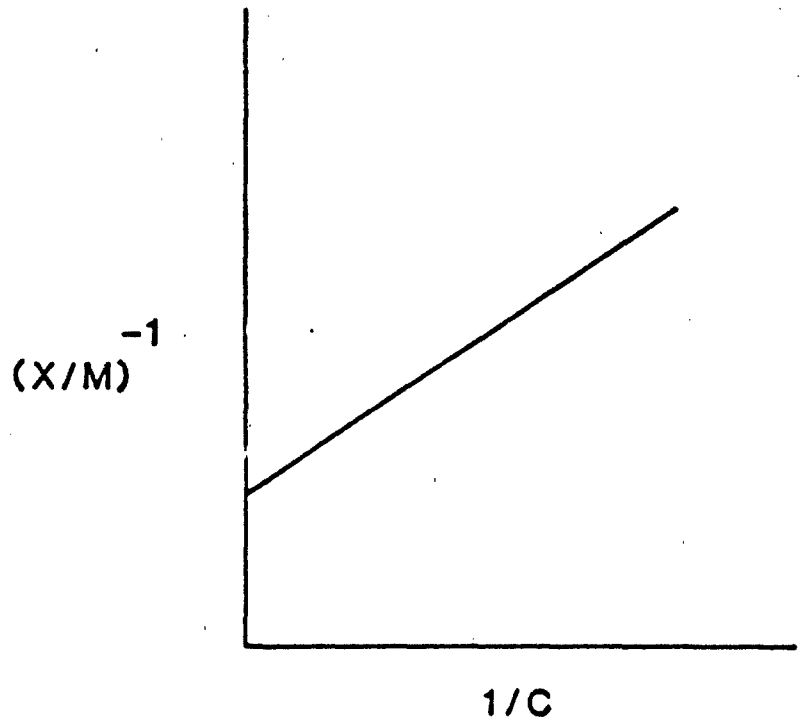


Figure 7. Linearized Langmuir isotherm. Where:
X = The weight of the adsorbed substance,
M = The weight of the adsorbent,
C = The equilibrium concentration of contaminant.[8]

c. The second and further layers are not affected by the binding forces acting on the first adsorbed layer. Thus, these layers have the same properties as in the liquid state.

A generalized graph of the BET is represented in Figure 8; the symbols are the same as in Figure 6. The BET isotherm takes the form[8]

$$q_e = \frac{BCQ^o}{(C_s-C)[1 + (B-1)(C/C_s)]} \qquad \text{(Equation 14)}$$

Where: q_e = the number of moles of solute adsorbed per unit weight at concentration C,
C = measured concentration of the solute at equilibrium,
C_s = saturated concentration of the solute,
Q^o = the number of moles of solute adsorbed per unit weight of adsorbent in forming a complete monolayer on the surface,
B = a constant expressing the energy of interaction with the surface in question.

The BET in linear form is

$$\frac{C}{(C_s-C)qe} = \frac{1}{BQ^o} + \left(\frac{B-1}{BQ^o}\right)\left(\frac{C}{C_s}\right) \qquad \text{(Equation 15)}$$

which takes the form (upon plotting) as shown in Figure 9.

In summary, the Langmuir equation is based on the assumption that maximum adsorption corresponds to a saturated monolayer of solute molecules on the adsorbent surface, the energy of adsorption is constant, and no transmigration of adsorbate occurs in the plane of the surface. The BET isotherm assumes a number of layers of adsorbate molecules form at the surface and the Langmuir equation applies to each layer. Furthermore, the BET equation model assumes that a given layer need not be complete before subsequent layers initiate adsorption. Therefore the equilibrium conditions involve several types of surfaces in that there are a number of layers and molecules on each surface site. Also, the BET model will reduce to the Langmuir model when the limit of adsorption is a monolayer.[8]

Applications of Carbon

Activated carbon has been demonstrated to adsorb inorganics as well as organics. Maatman et al. report that when an electrolyte solution contacts activated carbon, the solute may simultaneously adsorb on the surface and be excluded from the liquid near the liquid-solid interface. The authors report the order of adsorption as[36,37]

cations: $H^+ > Al^{+3} > Ca^{+2} > Li^+, NA^+, K^+$
anions: $NO_3^- > Cl^-$

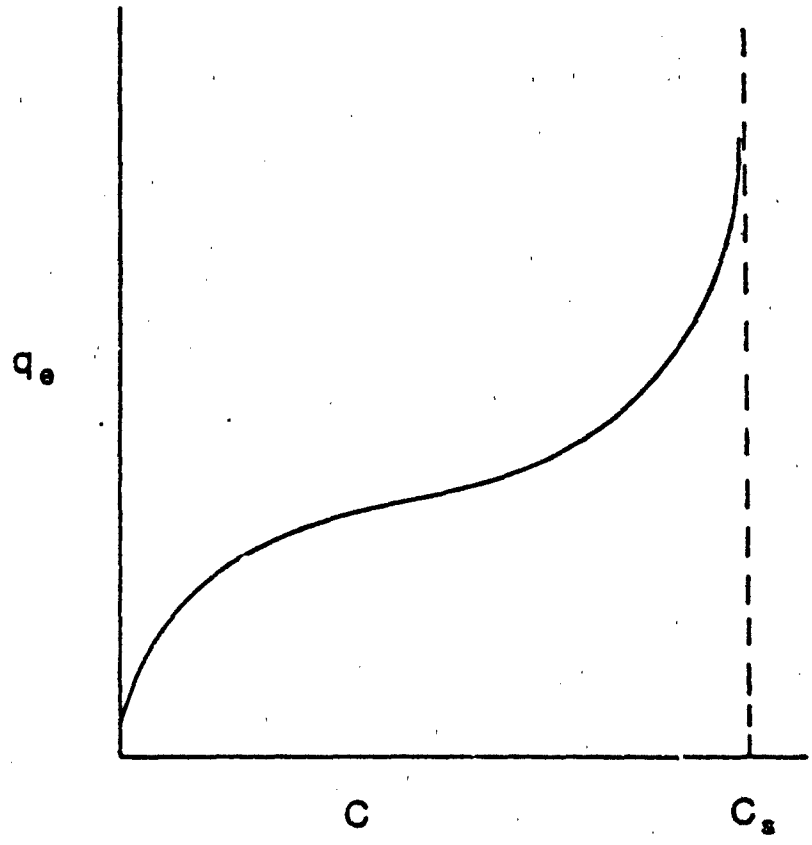


Figure 8. The Brunauer-Emmett-Teller isotherm.
Where:
q_e = The number of moles of solute adsorbed per unit weight adsorbent
C = The measured concentration of solution at equilibrium,
C_s = The concentration of the solution at saturation.[8]

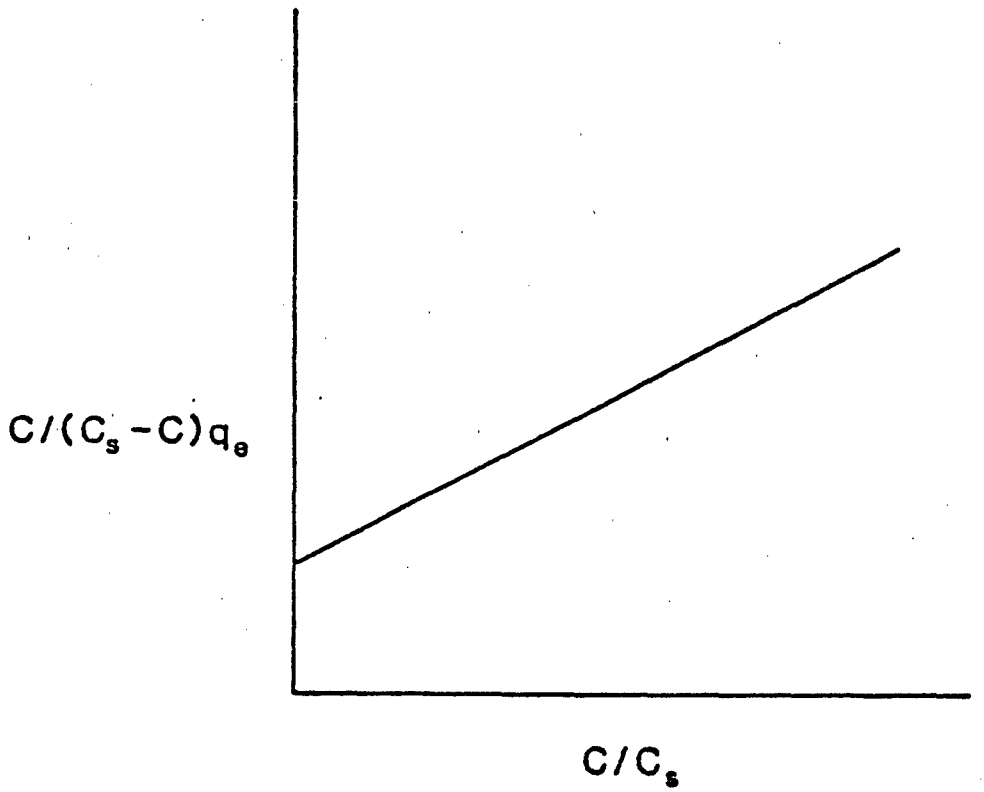


Figure 9. Linearized Brunauer-Emmett-Teller isotherm. Where:
C = The measured concentration at equilibrium of the solute,
C_s = The saturated concentration of the solute,
q_e = The number of moles of solute adsorbed per unit weight at concentration C.[8]

Although reports have appeared concerning the removal of inorganics, the main thrust of utilization of activated carbon is the removal of organics, especially refractory organics.

A number of authors state that activated carbon holds the most promise for treatment of wastewater and potable water to remove organics that are refractory to biological treatment.[5,38-40]

Eden and co-workers state that in wastewater treatment plants organics not susceptible to biological degradation were successfully removed by activated carbon. Furthermore, after long periods of use of the carbon (>60 weeks), bacteria were found in abundance, which led the authors to speculate upon "biological regeneration." "Biological regeneration" is the metabolism of adsorbed materials from active sites on the carbon, thus releasing the active sites for adsorption of solutes.[41]

Tebbutt et al. found that fatty acids and lipids were more efficiently adsorbed than were carbohydrates. In turn, carbohydrates were more efficiently adsorbed than were amino acids.[42]

Nupen and Stander have shown that activated carbon has no potential for virus or pathogenic bacteria removal.[43]

Outside of water treatment for potability or reuse, Kirk indicates that the food and pharmaceutical industries use activated carbon. In the food industry carbon is utilized for purification and color removal. The pharmaceutical industry uses activated carbon for removal of pyrogens from injectables, vitamin decolorizing, and insulin purification. Drug-quality carbon is administered orally to poison victims.[33]

REVERSE OSMOSIS

Historical

Reverse osmosis (RO) is a process whereby applied pressure is utilized to reverse normal osmotic flow across a semipermeable membrane (Figure 10).

The osmotic pressure is a property of the solution only, provided the membrane is truly semipermeable. The osmotic pressure then is a measure of some difference (as pressure) between the nature of the solution and that of the pure solvent.[9]

The first scientist to report on osmosis was Abbe' Nollet in 1748. During the 19th century Pfeffer first quantified osmosis by utilizing a semipermeable membrane of cupric ferrocyanide precipitated in the pores of porcelain. Pfeffer's data indicated that osmotic pressure is proportional to concentration of solute and absolute temperature. Van't Hoff recognized that osmotic pressure varied in the same manner as an ideal gas; from this observation the following relationship was described.[9,44]

$$\pi^{o} = \frac{\bar{n}}{V_m} RT \qquad \text{(Equation 16)}$$

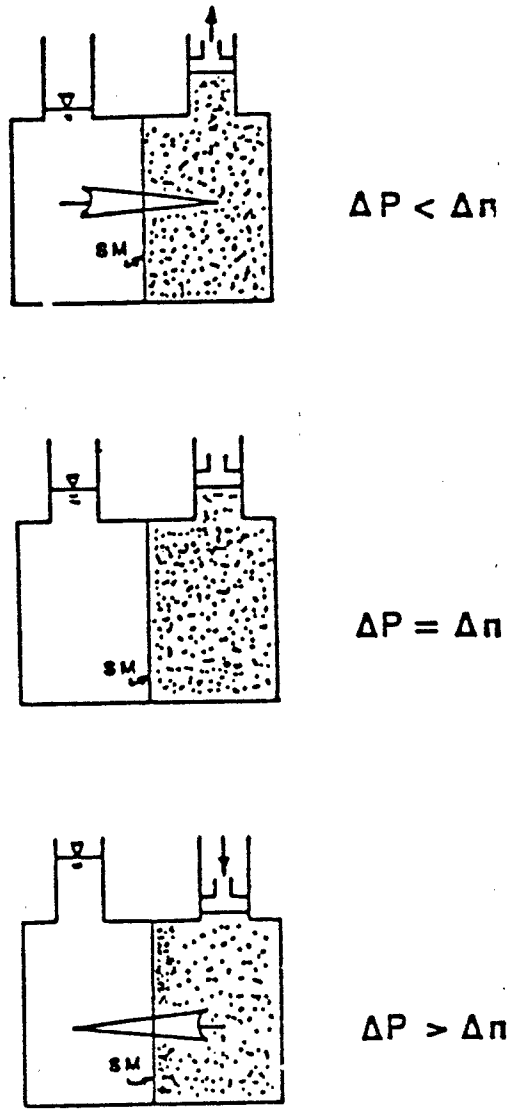


Figure 10. Osmotic flow across a semipermeable membrane (SM). Where:
ΔP = Applied pressure differential,
Δπ = Osmotic pressure differential.[9]

where: π^o = osmotic pressure
$\overline{n}$ = number of moles of solute
V_m = molar volume of solvent
R = gas constant
T = absolute temperature

Equation 15 is the Van't Hoff equation and is valid for dilute solutions. For more concentrated solutions, a modifier is introduced. The osmotic pressure coefficient (ϕ_c) varies with the solute concentration, and for most electrolytes it is less than unity, usually decreasing with increasing concentration.[9]

$$\pi^o = \phi_c \frac{\overline{n}}{V_m} RT \qquad \text{(Equation 17)}$$

Asymmetric or "skinned" membranes were manufactured as early as the 1930's in Europe and England. This led to a small but viable industry in the areas of ultrafiltration and microfiltration. However, the work that led to the modern membrane processing began in the 1950's with Reid's work on RO.[45] Concomitantly, but independently, Loeb and Sourirajan made the first high performance cellulose acetate RO membrane.[44] This was the first major breakthrough in RO technology. The Loeb-Sourirajan (L-S) study delineated methodologies to effectively cast very thin cellulose acetate membranes. The L-S RO membrane exhibited water fluxes an order of magnitude greater than any previously cast membrane. The L-S membrane is a "skinned" membrane in that it consists of a very thin salt-rejecting barrier of cellulose acetate integrally supported by a finely porous substrate. The high flux of the L-S RO is attributed to its extreme thinness.[46]

After the L-S RO was recognized for its great potential commercial success, the Office of Research and Technology (Dept. of the Interior) began to support research to delineate alternate polymers. Cellulose acetate was limited from the beginning due to its hydrolytic instability. Figure 11 represents the correlation between water permeability and salt permeability for various polymers.[47]

There are several factors that affect the useful life of an RO membrane, namely:[48,49]

(1) Pressure--The continuous yield of the membrane under pressure causes compaction, which in turn decreases the water flux but has no substantial effect on salt rejection.

(2) Biofouling--Some species of bacteria enzymatically attack cellulose acetate and destroy the dense top layer. This increases solute flux.

(3) Membrane Hydrolysis--RO membranes must be operated within the pH range of design. For example, cellulose acetate should be operated between pH 3-7. Above pH 7 and below pH 3 hydrolysis of the acetate radicals occurs and solute flux increases.

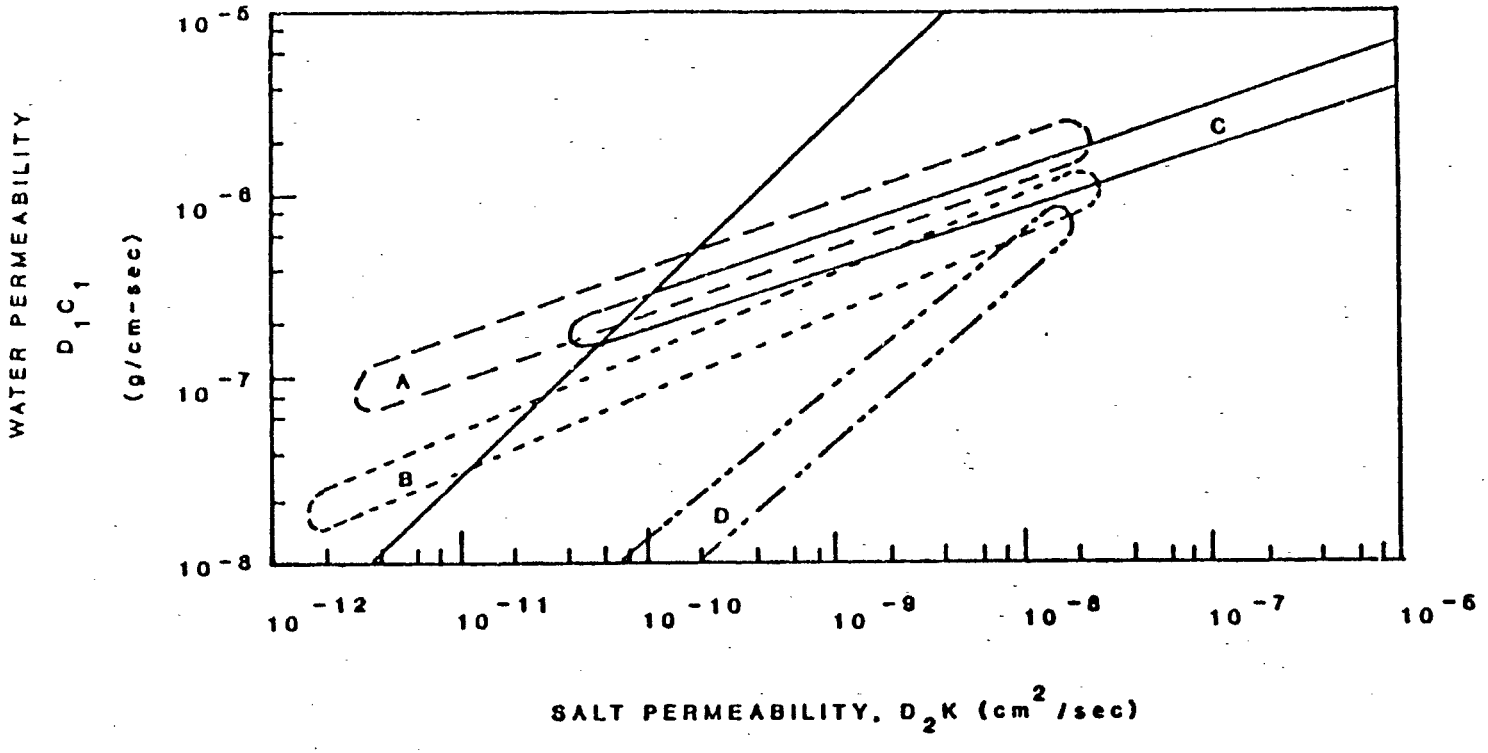


Figure 11. Correlation between the water permeability and the permeability to NaCl of several classes of polymeric membranes. A - cellulose acetates; B - ethyl cellulose-polyacrylic acid interpolymers; C - polyvinylpyrrolidone-polyisocyanate interpolymers; D - aliphatic polyamides.[47]

(4) Temperature--Temperatures above about 100°F damage membrane support structures and seals. As operating temperature increases, the membrane softens and compaction occurs. Also, temperature increases the rate of hydrolysis (Figure 12).

(5) Concentration Polarization--Coating of the membrane reduces water flux. Oils and salts near their saturation point may become supersaturated and precipitate over the membrane surface, which effectively increases $\Delta\pi$ at the membrane, which decreases $\Delta P-\Delta\pi$, thereby reducing the flux for any fixed pressure.

Membrane Manufacturing

The manufacture of RO membranes is a rather involved process. Since solvent permeability is inversely proportional to the path length (or membrane thickness), it is desirable to manufacture as thin a membrane as possible. The most definitive work presented on the subject of membrane casting was by Strathmann et al.[50] Strathmann was concerned with the cellulose acetate polymer; however, the description is applicable to membrane casting in general.

The casting of RO membranes utilizes four basic steps:[51]

(1) A solution of polymer in an appropriate solvent is cast in a thin film on a plate.

(2) An allotted amount of solvent is allowed to evaporate by timed exposure to the atmosphere.

(3) The membrane film is immersed and precipitated in a fluid bath (usually water) that is a nonsolvent for the membrane polymer but is miscible with the polymer solvent.

(4) The film is annealed by a timed exposure to hot water.

During the evaporation step, solvent is lost from the film surface and the polymer concentration in the surface areas is increased. During the third step, the water rapidly diffuses into the interior of the film. The water concentration exceeds the solubility of the polymer, and gelation occurs. The annealing stop shrinks the membrane and porosity decreases. It must be remembered that membrane casting is more of an art than a science.[51]

Strathmann described the above with a phase diagram. Figure 13 shows the composite phase diagram of a cellulose acetate membrane composition. The upper triangle represents cellulose acetate-acetone-water while the lower surface of the prism indicates acetone being replaced by formamide. All points within the prism represent mixtures of all four components. As indicated, cellulose acetate is slightly more soluble in an acetone-water mixture than in a formamide-water mixture.[50] If one takes a section through

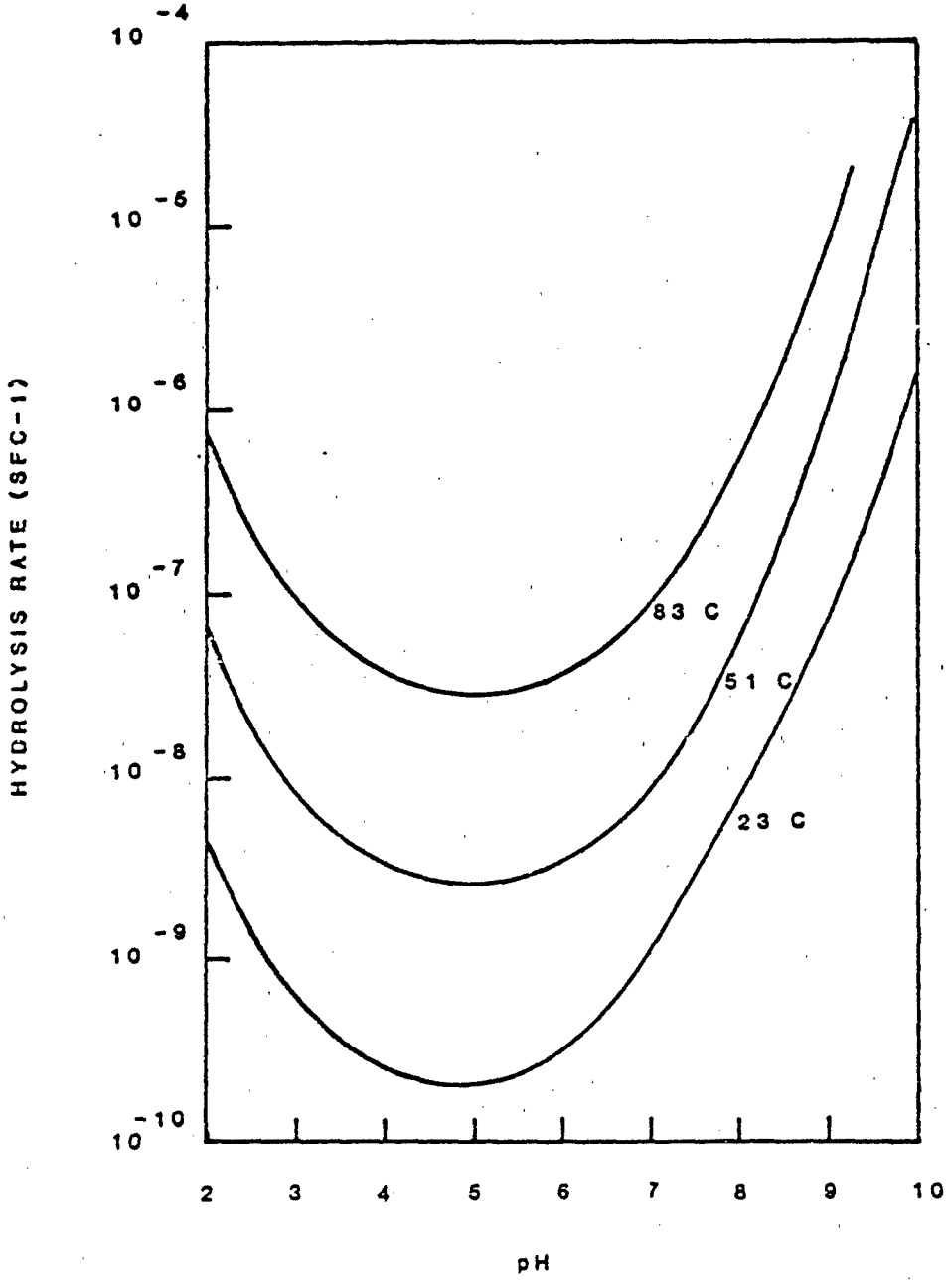


Figure 12. Hydrolysis of cellulose acetate reverse osmosis membranes over pH 2-10 at various operating temperatures.[49]

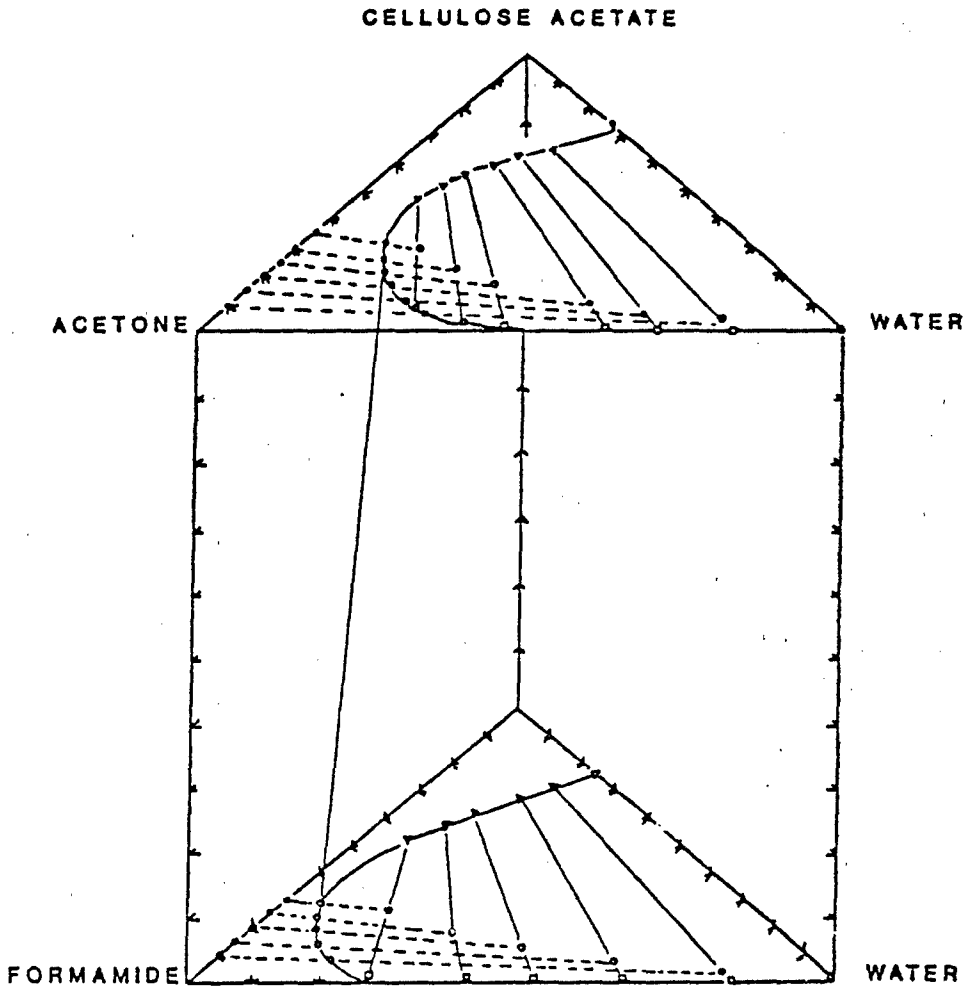


Figure 13. Phase diagram of the cellulose acetate-formamide-acetone-water system.[50]

Figure 13 at the acetone:formamide ratio of 6:4, Figure 14 results. The acetone-formamide mixture is labeled as "solvent."

When the membrane is precipitated by immersing the film into a water bath (step 3), the mixture concentration is diluted and solvent is lost from the casting solution composition to final membrane composition (represented by line AC in Figure 14). The resulting mixture at point C represents both a solid phase (S) and liquid phase (L) within the membrane pores.

Figure 15 represents some possible precipitation pathways at various ratios of water diffusing in and solvent diffusing out of the casting solution.

Evaporation During Membrane Casting

This step is critical in the manufacture of more retentive membranes. Solvent is lost mainly from the cast film surface, thus increasing the solids content. Figure 16 represents the effect of evaporation time on membrane salt rejection determined at 100 atm hydrostatic pressure with 1 percent sodium chloride.

Formation of Asymmetric Membranes

When an RO membrane is cast, the outermost surface is in direct contact with the water of the precipitation bath. The degree of supersaturation is extremely high. The density of the nuclei and their growth rate is high. The resultant is a finely dispersed structure that corresponds to the final membrane skin.

As the precipitation front moves further into the film, its composition becomes progressively richer in solvent and water has to diffuse through the already formed membrane skin into the precipitation zone. As the water concentration increases more slowly, thus lowering the degree of supersaturation, the precipitation becomes increasingly coarser. The average pore size increases from top to bottom of the membrane. A schematic representation is presented in Figure 17.

Membrane Annealing

Figure 18 indicates the effect of annealing temperatures on water flux and salt rejection. The reduction in pore sizes accompanying the shrinkage is probably responsible for the effects demonstrated in Figure 17. Another hypothesis concerns the restricted polymer mobility accompanying the increased degree of crystallinity. The increase in crystallinity markedly reduces the freedom of movement in the polymer chains.

The foregoing succession of treatment steps is necessary to ensure a well cast membrane with high water flux and high salt rejection.

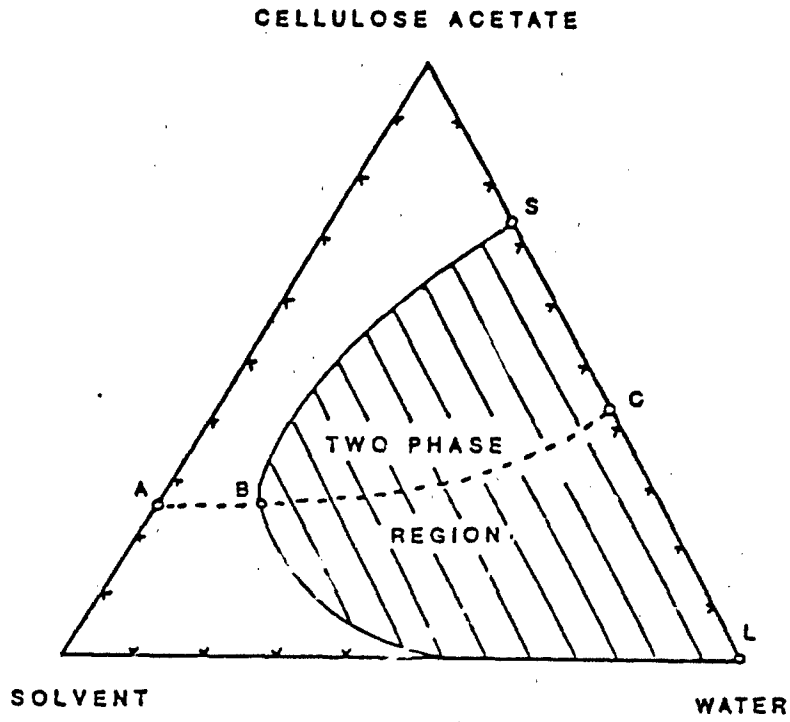


Figure 14. A section of the quaternary phase diagram shown in Figure 13. The term "solvent" represents a mixture of 40 wt-% formamide and 60 wt-% acetone.[50]

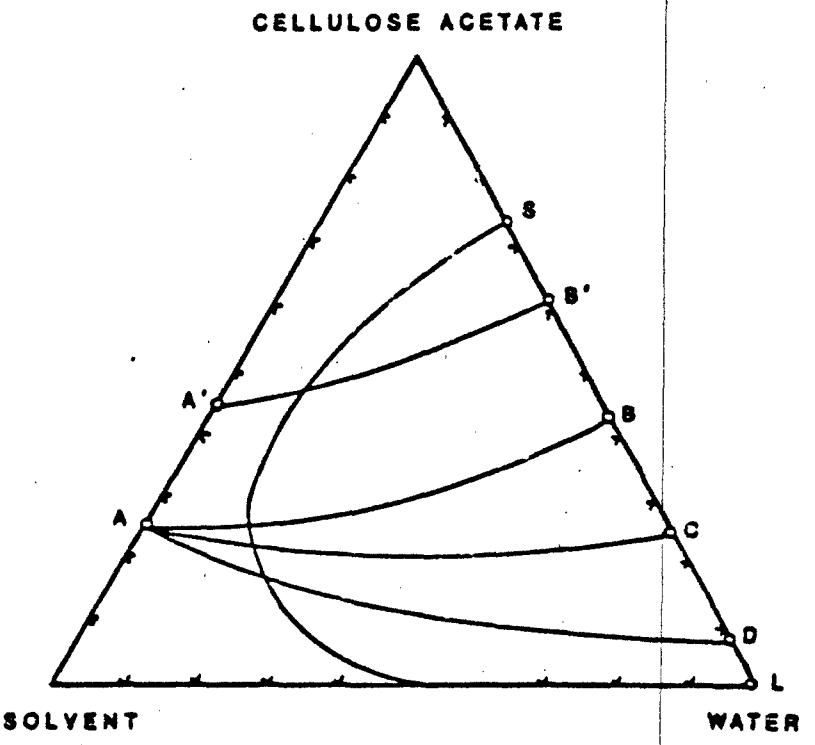


Figure 15. Phase diagram of the cellulose acetate-solvent-water system, showing the precipitation paths at various relative rates of water diffusing in and solvent diffusing out of the casting solution.[50]

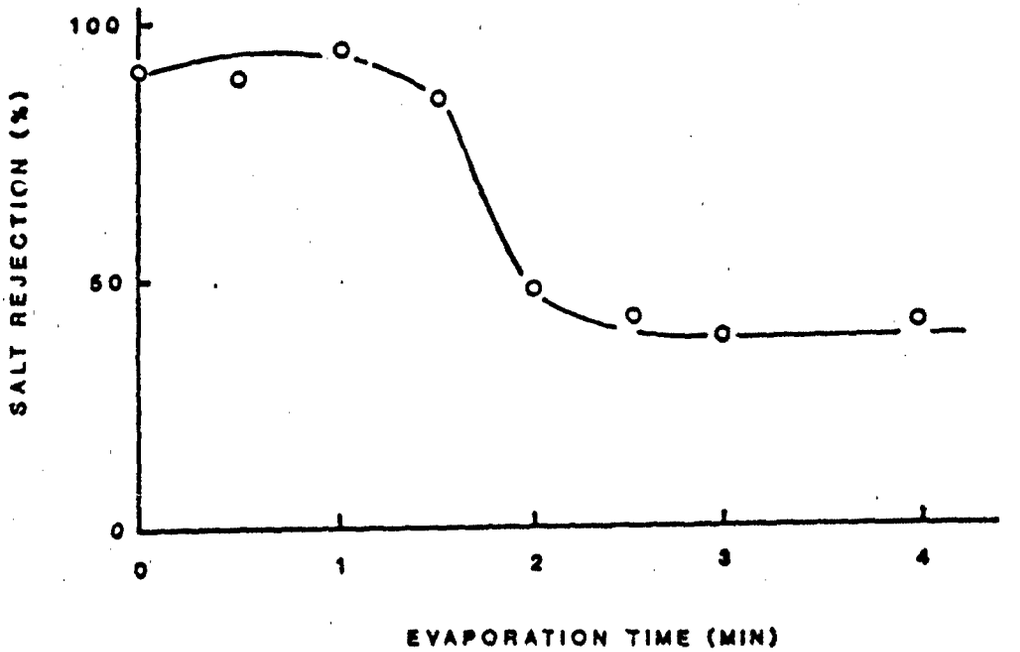


Figure 16. Effect of evaporation time at 25°C on salt rejection of a membrane cast from 25 wt-% cellulose acetate, 30 wt-% formamide and 45 wt-% acetone. The membrane was annealed for 2 minutes at 75°C.[50]

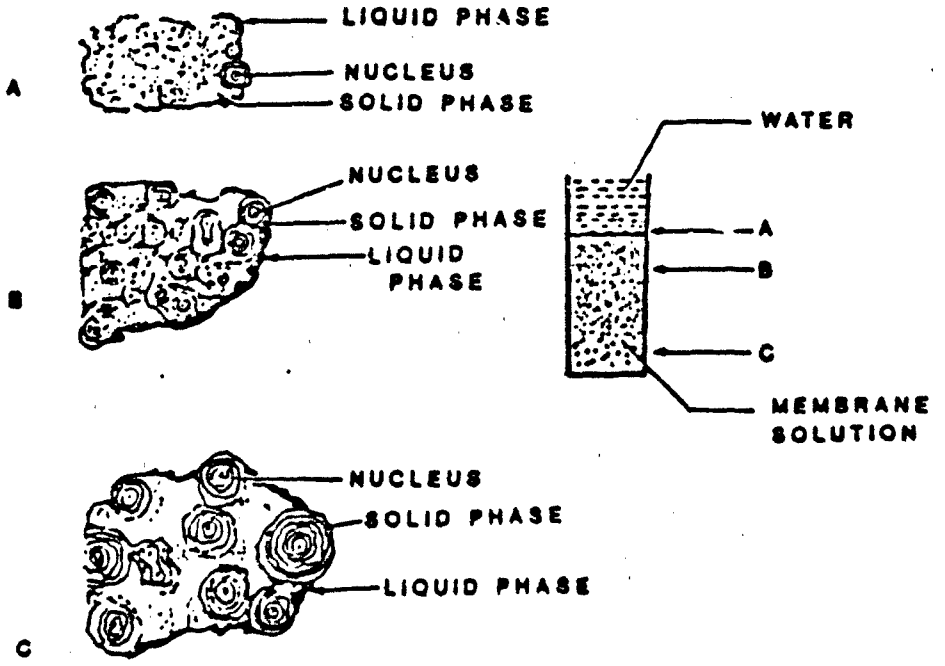


Figure 17. Schematic diagram of polymer precipitation at different points through a membrane cross section.
A - High supersaturation at the membrane surface; many nuclei and rapid growth.
B - Lower supersaturation; fewer nuclei and less rapid growth.
C - Low supersaturation; few nuclei and slow growth.[50]

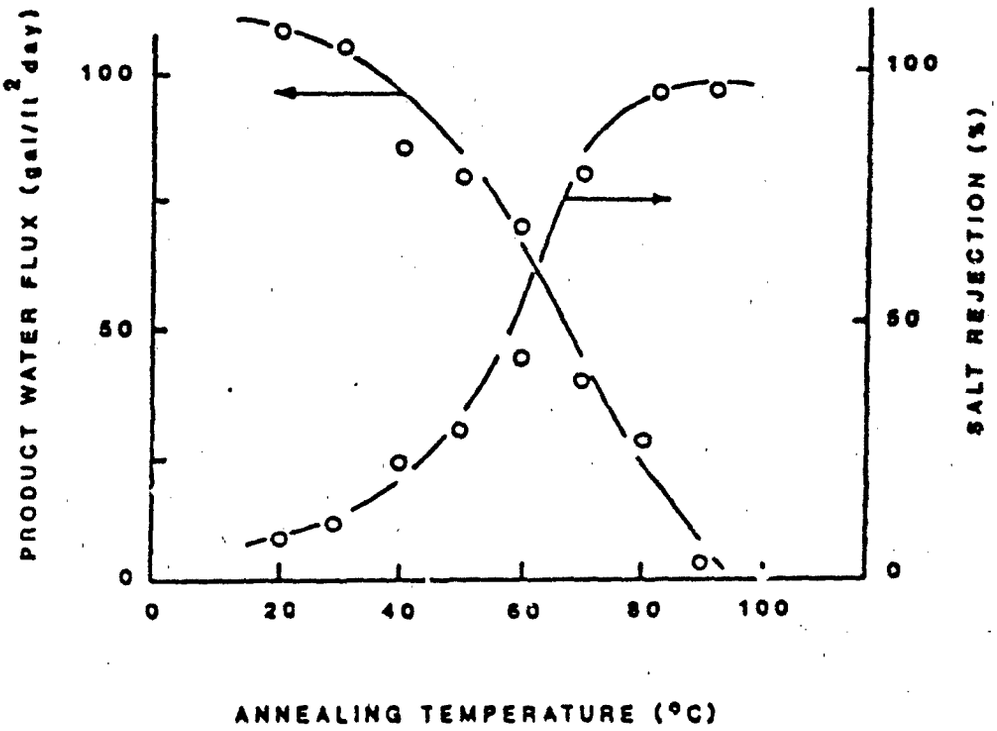


Figure 18. The effect of annealing temperature on the retention and flux of membranes cast from 25 wt-% cellulose acetate, 30 wt-% formamide and 45 wt-% acetone. Evaporation time was 2 minutes at 25°C.[50]

Configuration of Membranes

Figure 19 schematically represents the four main module designs.

The earliest type of membrane configuration was the simple plate and frame. The membrane was merely supported between two plates with an exit provided for the reject and permeate flows.

The tubular design necessitates a large volume of input water due to the diameter (10-25 mm).

By far, the most commonly used configurations are either the spiral wound or the hollow fine fiber. The packing densities are a function of membrane size. For example, hollow fine fiber (80 microns O.D.) modules are densely packed with 5,000 ft^2/ft^3 as compared to spiral wound modules of 250 ft^2/ft^3.[43]

Table 4 indicates a comparison of characteristics and configurations. When selecting a membrane-type module configuration, one must consider the quality of input water and the degree of pretreatment necessitated.

For example, the hollow fine fiber produces more flux than does the spiral wound. However, the physical nature of the hollow fine fibers makes them quite susceptible to fouling by turbid water whereas the spiral-wound modules are much more resistant.[46,48]

Solvent Transport

The two leading theories concerning solvent transport across an RO membrane were advanced by Sourirajan[52] and by Lonsdale.[53]

Sourirajan advanced a "preferential sorption capillary flow" mechanism, according to which, RO is a result of preferential sorption of one of the constituents of the fluid mixture at the membrane-solution interface and fluid permeating through the microporous membrane.

Basically, two criteria must first be met: 1) a membrane surface of an appropriate chemical nature must be in contact with the feed solution, and 2) the pores on the membrane surface must be both of appropriate size and of sufficient number. Both of the criteria must be met for the success of the separation process.

The term "preferential sorption" refers to the existence of a steep concentration gradient at the membrane-solution interface. The terms "pore" and "capillary" refer to any void space connecting the high and low pressure sides. A schematic representation is shown in Figure 20.

For RO separation to take place, one of the constituents must be preferentially sorbed at the interface. The successful RO membrane is microporous and heterogeneous at all levels of solute separation. The surface must be as thin as possible to reduce resistance to fluid flow. Also, the overall porous structure of the membrane must be asymmetric.

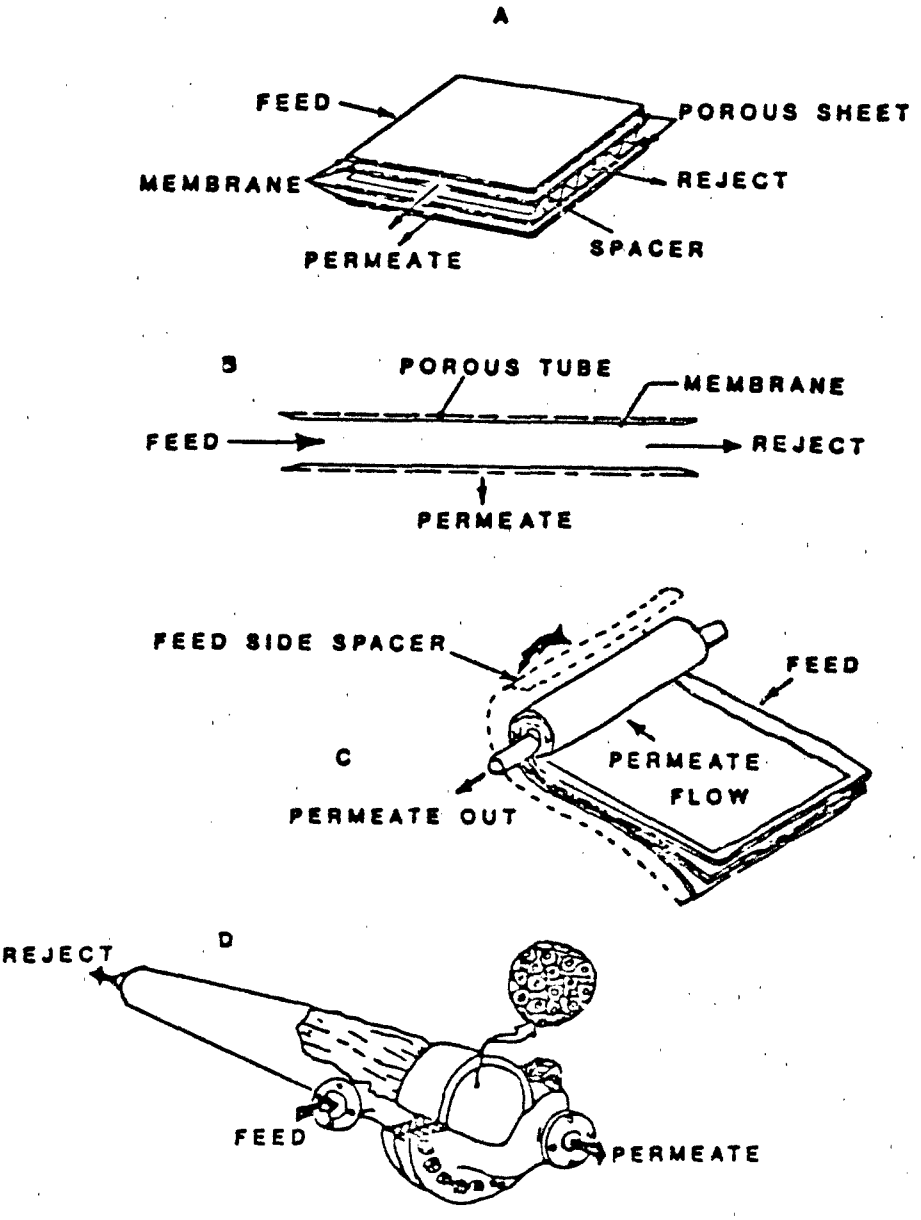


Figure 19. Schematic representation of the four main reverse osmosis module designs.
A - Plate and frame; B - Tubular;
C - Spiral wound; D - Hollow fibers.[44]

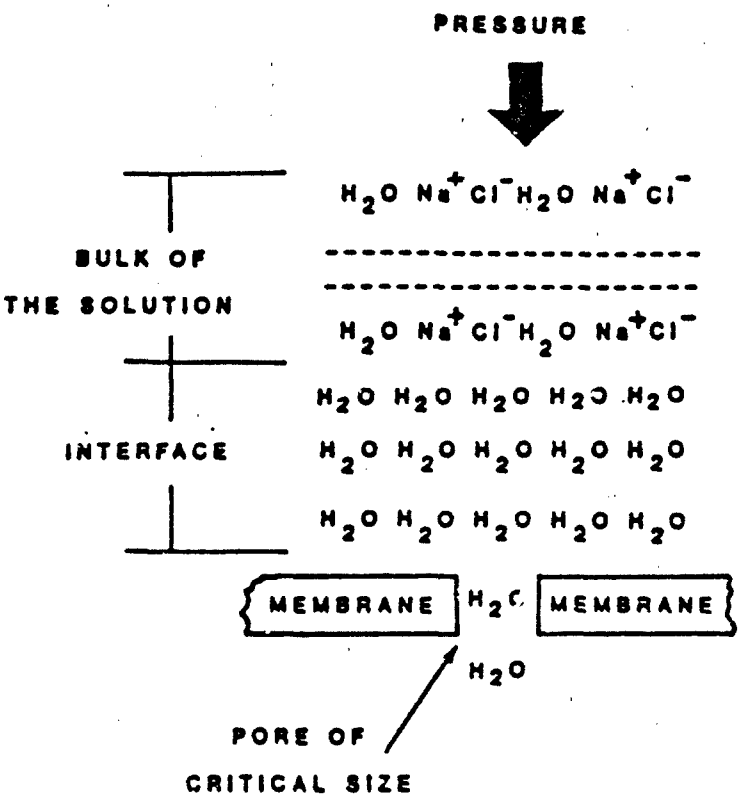


Figure 20. Schematic representation of Sourirajan's preferential sorption capillary flow mechanism.[52]

TABLE 4. REVERSE OSMOSIS MEMBRANE COMPARISON

Characteristic	Configuration		
	Hollow Fiber	Spiral Wound	Tubular
Flux and Rejection Range	High	High	High
pH Range Tolerance	4-10	4-7	4-7
Production per Unit Space	Excellent	Good	Fair
Resistance to Fouling	Low	Medium	High
Ease of Cleaning	Fair	Good	Excellent
Cost Ratio/1000 gals-capacity	Low	Low	Higher
Operating Pressure (P.S.I.)	400-450	400-600	400-800

There is a critical pore diameter for maximum solute separation and fluid permeability. The magnitude for the critical pore diameter is a function of the strength and magnitude of the preferential sorption forces at the membrane-solution interface. Therefore, RO is not a size separation by sieve filtration.[51,52]

Sourirajan further explained the criteria for preferential sorption in the context of Lowry-Brønsted proton donor-acceptor. The cellulose acetate molecule acts as a net proton acceptor (base). A solute that is a proton donor (alcohols, phenols, acids) is attracted to the membrane. Conversely, solutes such as aldehydes, ketones, esters and ethers are proton acceptors, and are therefore repelled from the membrane surface. Consequently, lower acidity increases preferential sorption of water at the membrane-solution interface. When the acidity of the solute is less than that of water, the latter is preferentially sorbed. Conversely, when the acidity of the solute is more than that of water, the solute is preferentially sorbed.

Lonsdale makes the argument for a process he terms "solution-diffusion." Solution-diffusion is a process in which permeation occurs via the dissolution of the permeates in the polymeric membrane material and the subsequent diffusion down their concentration gradient.[44,47,53]

According to a homogeneous solution diffusion model, solvent (water) permeate flux through a semipermeable membrane of a given thickness is given by:[9,53]

$$F_w^o = \frac{D_{l,w}^o \; C_w \; V_m}{R \; T \; \delta m} \; (\Delta P - \Delta \pi^o) \qquad \text{(Equation 18)}$$

Where:
- F_w^o = Water flux across the membrane
- $D_{l,w}^o$ = The effective diffusion coefficient in the membrane
- C_w = The concentration of water in the membrane
- V_m = The molar volume of water
- R = Gas constant
- T = Absolute temperature
- δ_m = Membrane thickness
- ΔP = The difference in driving pressure across the membrane
- $\Delta \pi^o$ = The difference in osmotic pressure across the membrane

If the effective diffusion coefficient of water in the membrane, the concentration of water, and the molar volume of water are independent of pressure (reasonable assumption up to 140 atm), then the water flow rate per unit membrane area is directly proportional to the driving pressure ($\Delta P - \Delta \pi^o$).

The coefficient $\frac{D_{l,w}^o \; C_w \; V_m}{RT \; \delta m}$ indicates that water flux is inversely proportional to the membrane thickness. The coefficient is usually represented as W_p. Equation 18 reduces to

$$F_w^o = W_p \; (\Delta P - \Delta \pi^o). \qquad \text{(Equation 19)}$$

Solute flux also follows the solution-diffusion model. However, the driving force is almost entirely due to the concentration gradient across the membrane.

$$F_i^o = D_{l,i}^o \; \frac{dC_{im}}{dx} = D_{l,i}^o \; \frac{\Delta C_{im}}{\delta m} \qquad \text{(Equation 20)}$$

where: F_i^o = Solute flux

$D_{l,i}^o$ = The effective diffusion coefficient of solute

C_{im} = The concentration of species i within the membrane

ΔC_{im} = Concentration gradient of species i taken across the thickness of the membrane

δm = Membrane thickness.

x = Direction perpendicular to membrane

Equation 20 may be stated in terms of concentrations of the solutions, C_i, on either side of the membrane by utilizing the distribution coefficient K_d (K_d is usually constant in the range of interest for cellulose acetate membranes).

$$F_i^o = D_{l,i}^o K_d \frac{\Delta C_i}{\delta m} = K_p \Delta C_i \qquad \text{(Equation 21)}$$

where: K_p = The coefficient of permeability for species i.

The coefficient of permeation (W_p) and the solute-permeability coefficient (K_p) are characteristics of a particular membrane composition and method of manufacture.

Equation 18 indicates that water flux is dependent upon net pressure differences while Equation 20 indicates that solute flux is concentration dependent. Also indicated is that quality of the permeate decreases with increased solute concentration in the feed water. This effect is caused by an increase in the feed osmotic pressure as more solvent is drawn off; the solute becomes more concentrated at the membrane surface and a decrease in flux is observed.

The build-up of solutes on the membrane surface is termed concentration polarization. This solute build-up exceeds the feed solution concentration and a concentration gradient is then established. The solute diffuses back into the feed solution along the gradient.

Concentration polarization produces several undesirable effects:[11]

(1) Raises the local osmotic pressure, which reduces the water flux,

(2) Increases the solute content in the permeate,

(3) With certain solutes, may accelerate membrane deterioration,

(4) Increases the probability of precipitation of sparingly soluble salts on the membrane surface.

Concentration polarization is defined as the ratio of salt concentration at the membrane surface to the salt concentration in the bulk or feed stream.[54,55]

Equation 22 describes concentration polarization at any point along the feed channel.

$$\frac{F_w^o C_{ic}}{C_{w_c}} - D_{l,i} \frac{dC_{ic}}{dx} = K_p \Delta Ci \qquad \text{(Equation 22)}$$

where: F_w^o = Water flux
C_{ic} = Concentration of ith substance in the concentrate stream
C_{wc} = Concentration of water in the concentrate stream
$D_{l,i}$ = Free liquid diffusion coefficient
x = Direction perpendicular to membrane
K_p = Coefficient of solute permeability
ΔC_i = Difference in concentration of solutions on either side of the membrane

The first term represents the contribution of bulk flow in solute flux toward the membrane. The second term represents the diffusive back flux of solute from the membrane. The right-hand side is the flux of solute through the membrane.[9]

Concentration polarization permits the build-up of salts with low diffusion coefficients. Colloidal fouling is most probably an outgrowth of this effect, since colloids have diffusion coefficients of two to three orders of magnitude lower than brackish water salts.[9] Figure 21 is a schematic representation of concentration polarization.

The polarization problem is corrected, as far as possible, by maintaining a high fluid flow over the membrane surface. The resulting turbulence reduces the thickness of the secondary layer.[44,54,55]

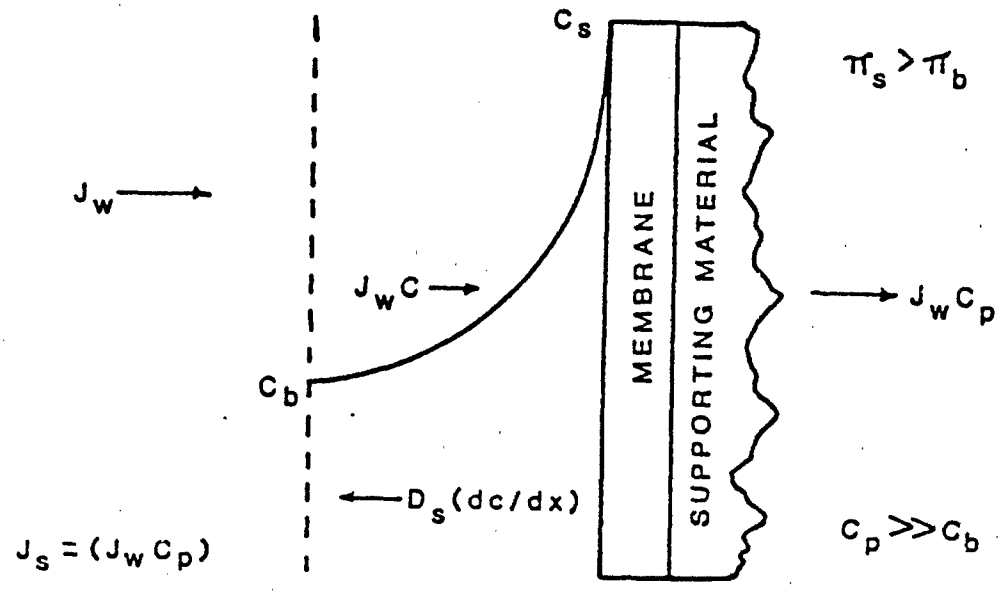
General

Much of the application of RO has been in the areas of desalination of seawater[56-67] and of water reuse.[56,60,61,68]

Carnahan designed and subsequently type-classified a field water treatment system for the U.S. Army.[64] The system, termed the ROWPU (Reverse Osmosis Water Purification Unit) is capable of desalinating seawater and brackish water in addition to the treatment of freshwater for potable purposes.

The offshore drilling industry utilizes RO for potable water production. Lerat found RO with hollow fine fibers capable of reducing an average of 35,000 ppm total dissolved solids (TDS) to approximately 500 ppm TDS. However, due to the ease of fouling of the hollow fibers, the RO section of the system was preceded with an adequate turbidity removal treatment section.[66]

Tan et al. found in their work that polybenzimidazole (PBI) thin film composite membranes had high flux values (50 gfd) with 90 percent salt rejection initially. However, pressure-induced compaction caused a decrease with time.[65] Experimental results of Tan et al. agree with Morris in that the PBI thin film composite is economical and has proven its efficacy in seawater desalination.[65,67]



$$J_w = K_m(\Delta P - \Delta \pi)$$

Figure 21. Schematic representation of concentration polarization at the membrane surface: Where:

J_w = Water flux,
J_s = Solute flux to the membrane = $J_w C_p$,
C = Concentration of membrane retained solute,
C_p = Concentration of solute in the permeate,
C_s = Concentration of solute retained at the membrane surface,
C_b = Concentration of solute in the bulk solution,
D_s = Diffusion coefficient of retained species,
K_m = Membrane permeability,

π_s = Osmotic pressure at the surface of the membrane,
π_b = Osmotic pressure at the bulk stream.[55]

Another rapidly growing area of RO application is in the arena of water reuse. In 1981, a 5-day seminar entitled Water Reuse with its theme of "Water Reuse in the Future" was held in Washington, DC. Of all technologies discussed, membrane filtration was the most promising.[56]

Reverse osmosis significantly removes Escherichia coli from waste streams, more than five orders of magnitude.[57] Chian et al. determined that if properly employed, RO reduces the ozone demand and concomitantly the total organic carbon in the permeate. Furthermore, the permeate contained only organics of less than 150 molecular weight.[58] The treatment of a waste stream by membrane filtration is successful enough to permit the permeate to be released into waterways.[59]

However, there are still areas to be addressed to enhance the successful utilization of RO technology. Many membrane compositions are susceptible to microbial attack, hydrolysis, and compaction.[60,61] Wechsler concluded that to circumvent membrane fouling problems, the feed water must be improved as extensively as possible.[62] That is, a mere turbidity filter cannot be the sole feed-water treatment unit in an RO system.

Reverse osmosis has considerable application in the pharmaceutical industry for the manufacture of sterile non-pyrogenic water. Reverse osmosis retains viral as well as bacterial particles on the membrane surface, thus producing sterile water.[63] The medical device industry utilizes RO because of the economies of the system as compared to distillation. Not only is the initial capital investment less, but RO lends itself to chemical sterilization of equipment with either chlorine or formaldehyde.[69]

According to Blais et al., developmental research with new polymers has enabled kidney and peritoneal dialysis patients to remain at home rather than undergo frequent and costly trips to hospitals.[70]

Reverse osmosis is the ultimate membrane filtration methodology. The applications range from potable water production to waste stream treatment to meet release standards to medical applications.

LIMULUS AMEBOCYTE LYSATE

Historical

Endotoxins or lipopolysaccharides (LPS) are products of gram negative bacteria, from the family Enterobactericae. The LPS, which is the outer cell membrane, is bound to the core polysaccharide by the lipid A moiety.[71]

When LPS is introduced into a host (Figure 22), especially intravenously, production of endogenous pyrogens is elicited in response to the exogenous pyrogens.[72] According to Cluff, LPS have the capacity to alter the susceptibility to infection, i.e., the LPS may enhance the pathogenicity of the infection.[73]

Therefore, the pharmaceutical industry considers contamination of large volume parenterals (LVPs), small volume parenterals (SVPs), or medical devices with LPS to be of paramount importance. If any of the above products become contaminated with LPS and introduced to an already traumatized patient, damage

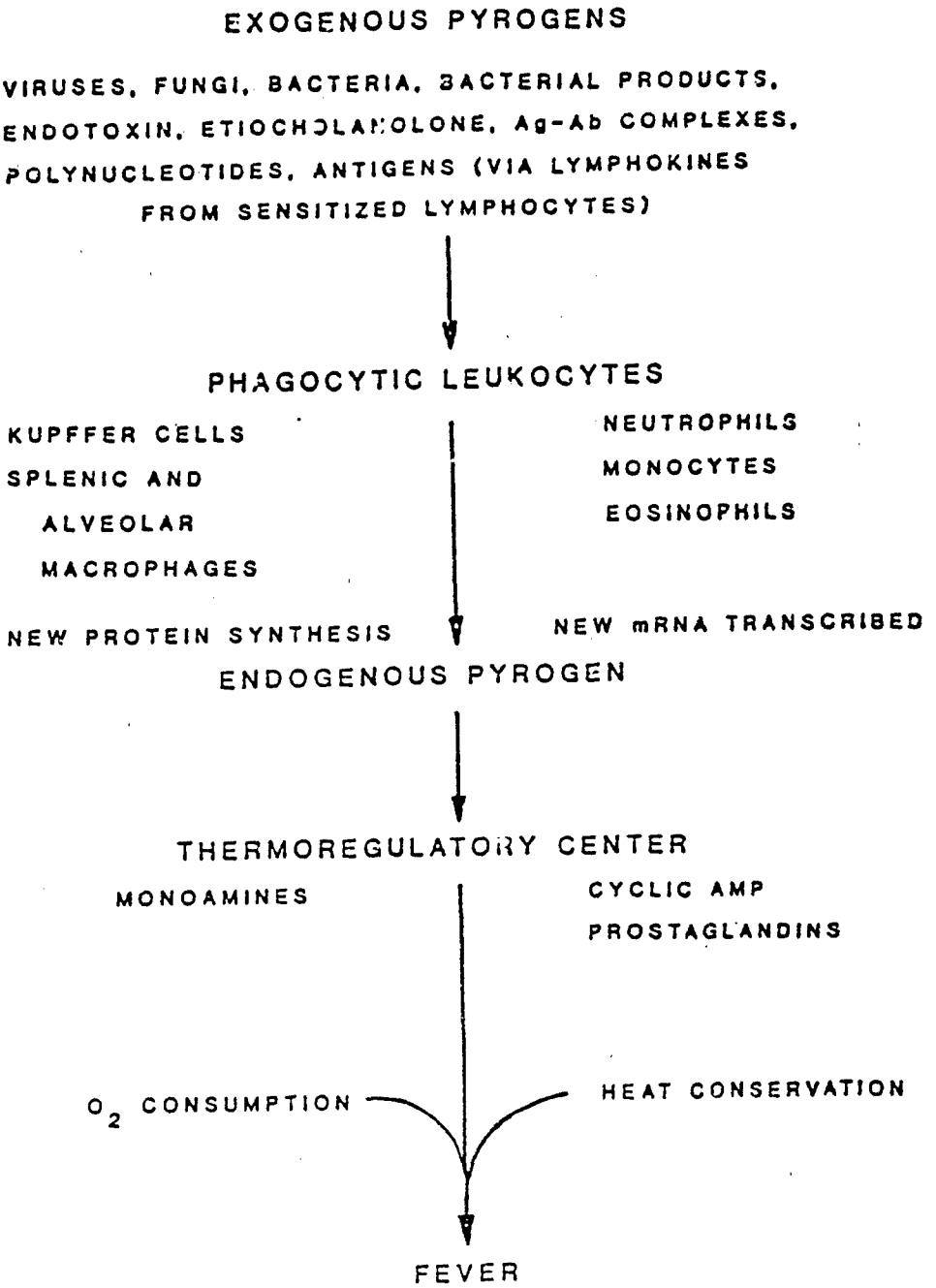


Figure 22. Schematic diagram of the chain of events culminating in the manifestation of fever in a host after the introduction of exogenous pyrogens.[72]

to life support organs and death may ensue. Until recently, the quality control/quality assurance for the pharmaceutical industry was the USP rabbit test.[4]

The following is extracted from the USPXX concerning the USP rabbit test.

> The pyrogen test is designed to limit to an acceptable level the risks of febrile reaction in the patient to the administration, by injection, of the product concerned. The test involves measuring the rise in temperature of rabbits following the intravenous injection of a test solution and is designed for products that can be tolerated by the test rabbit in a dose not to exceed 10 mL per kg injected intravenously within a period of not more than 10 minutes.

See Appendix C for a description of the USP rabbit test.

In 1956, Bang discovered a system in the hemolymph of the horseshoe crab, Limulus polyphemus, that sequestered microbial invaders and prevented infection.[74] Bang and Levin described this phenomenon and correlated it with the presence of circulatory amebocytes that mediated the clotting of the Limulus blood.[75]

Bang's discovery has led to the current state of the art for LPS pyrogen testing via the Limulus amebocyte lysate (LAL) test. The first generation of LAL was a gel precipitation test.[76] The LAL gel test utilized dilutions involving discrete data points. Therefore, the end point was a qualitative assessment between the last positive dilution point and the first negative dilution point.

After the delineation of the coagulogen, a new generation of tests evolved, which utilizes spectrophotometric methodology and is therefore continuous. The chromogenic method lends itself to rapid quantitation with greater precision and accuracy than are afforded by the gel test.[77,78]

The USP Rabbit Test vs. the LAL Test

As previously stated, the USP rabbit test has been the official pyrogen test for approximately 40 years (see Appendix C). Before the Bureau of Biologics would approve a replacement test through the Federal Drug Administration (FDA), much investigation was performed on exogenous pyrogens and the USP rabbit test versus the LAL test.

As to the USP rabbit test, Pearson et al. claimed that the one greatest problem was the variability of animals within a colony and from colony to colony.[79] Further variability occurs according to the test method utilized. Rabbits restrained in a prone position showed a greater rise in rectal temperatures than rabbits in a supine position when challenged intravenously (IV) with 10 µg/kg of Escherichia coli pyrogen.[80]

Another USP rabbit test inadequacy involves the regulatory samples sent to the FDA. A statistical study concluded that "possibly the rabbit test is

unsuitable to detect types of pyrogens that might be encountered in regulatory samples."[81] That is, the pyrogen levels in regulatory samples have been screened, and the samples higher in pyrogen have been eliminated. This would leave samples with an increased probability of a Type II error (rejecting a nonpyrogenic sample).

When the LAL test was compared by Cooper et al. to the USP rabbit test, with an LPS concentration of 0.001 µg/mL from E. coli and 0.0001 µg/mL from Klebsiella sp., the USP rabbit test results were negative while the LAL test was positive for LPS. The data led the authors to conclude that the LAL test is an order of magnitude more sensitive than the USP rabbit test.[81,82]

Pericin reported that a good correlation existed between the USP rabbit test and the LAL test, especially with respect to the testing of pharmaceutical water, with the LAL being more sensitive.[83] Didig claims that based upon available data, the USP rabbit test is far from ideal, the LAL test is more sensitive, more rapid, less expensive, and can be accepted as the final quality check on LVPs.[84]

The USP rabbit test is primarily dose dependent (volume/kilogram) whereas the LAL test is concentration dependent. A 1-hour incubation LAL test is conservatively twice as sensitive as a rabbit test at a threshold dose of 10 mL/kg.[85]

According to Pearson, a variety of organic compounds are capable of producing pyrogenic responses in man; however, studies have shown that bacterial endotoxins are the only pyrogens of significance.[86,87] Echoing Pearson, Mascoli has stated that the concern should be with the relative insensitivity of the USP rabbit test than with the rarely, if ever seen, cases of non-LPS pyrogens.[88]

The LAL test is a reliable and, probably of more importance, a reproducible method to ascertain the presence of LPS contamination. Travenol Drug Co. has enough faith and, more germane, statistics to validate the LAL test as an in-house quality control test and a final release test.[87,89-91]

The standard for the LAL test to reject an LVP has been tentatively set at 5 EU (Endotoxin Units, where 0.2 ng LPS = 1 EU). This limit resulted from tests initiated by the Bureau of Biologics after 56 independent laboratories performed tests utilizing a reference LPS.[92] This correlates with a study undertaken by Dabbah et al., performed in 1980. The authors' findings were that it was reasonable to set the limit around 0.1 ng/mL as the standard, because the LAL test has a failure (reject) significantly greater than 50 percent at this concentration. The authors further stated that under these conditions the LAL is considered equivalent to the USP rabbit test.[93]

The Biochemistry of the Limulus Lysate

Since the aforementioned discovery by Bang and Levin, there has been much work directed towards the delineation of the molecular mechanisms involved in clotting.

The Limulus lysate possesses a proenzyme that, when activated by LPS, catalyses the gelation of the coagulogen (clottable protein). The proenzyme

has a molecular weight of approximately 150,000 and requires both calcium and LPS for activation.[94,95] Column chromatography isolated two major proteins, 79,000 and 40,000 molecular weight peptides, which suggests a monomer-dimer relationship.[95,96] Upon incubation of either peptide with LPS and coagulogen, a gel clot failed to form.[96]

Belief that the enzyme itself is a serine protease (trypsin-like) is based on the effects on it of diisopropylfluorophosphate, phenylmethylsulfonyl fluoride and soybean trypsin inhibitor.[96,97] The active enzyme (heat labile and pH sensitive) has a molecular weight in the neighborhood of 150,000, and it is considered to be a single polypeptide chain.[98] Once the enzyme is activated in an appropriate manner, it then acts upon the coagulogen to form the gel clot. While the enzyme is thermolabile, the coagulogen is thermostable.[98]

Several investigators have determined the coagulogen to be a peptide of approximately 25,000 molecular weight.[95,98-100] Upon enzymatic hydrolysis, a peptide of approximately 7,000 molecular weight is released before the larger fragment undergoes the subsequent clot formation.[98] The coagulogen is cleaved between the amino acids arginine and lysine, to yield the smaller C-peptide of 45 amino acids and a larger N-peptide of 175 amino acids.[95] The larger N-peptide contains all disulfide amino acids, which form non-covalent bonds with other N-peptides to produce the gel clot.[95]

The LPS Molecule and Reactivity with LAL

The LPS molecule may be divided into three distinct units:[101]

(1) O-Polysaccharide moiety: Determines the antigenic specificity.

(2) R-Core: The mid-region of the LPS molecule. The R-core links the O-polysaccharide with the lipid A moiety.

(3) Lipid A Moiety: The entity responsible for leucocytosis, complement activation, and pyrogenic response.

Rickles et al. demonstrated lysate specificity to lipid A by utilizing polymixin B (a cyclic peptide that binds lipid A) to inhibit the lysate-LPS reaction.[102] Rostram-Abadi and Pistole indicated that the compound 2-keto-3-deoxyoctonate (KDO) is the possible imuno-determinate group in the core region of Enterobacteriaceae. The KDO molecule occupies the innermost sugar residue position in the core polysaccharide and provides a point of attachment to the lipid A moeity. The authors demonstrated that free KDO inhibited the precipitation reactions.[103]

The sensitivity of the lysate to the LPS is a function of the following:[104,105]

1. The source of LPS; reaction rates vary from species to species of the Enterobacteriaceae.

2. The method of LAL preparation (cell lysis versus freeze thawing).

3. The method of assay, i.e., slide agglutination, gel clot or turbidimeteric.

As previously stated, the LAL test is specific for the species of the Enterobactericae family. The lysate has been demonstrated not to react with gram positive bacteria, yeast, most other gram negative bacteria and toxins.[106-108] With the sensitivity of the LAL test greater than the USP rabbit test, coupled with the methodology of the LAL test, the LAL test lends itself readily to a field test.

EXPERIMENTAL PROCEDURES

To accomplish the objective, the research was performed in two phases. Phase one involved construction of a test stand and testing of individual filtration methodologies under consideration. Phase two consisted of combining the selected filters into a system and utilizing the system to produce WFI.

Phase I. Figure 23 describes the test stand, challenge water tank, and pump utilized throughout the course of the individual filter evaluations. With the exception of the reverse osmosis membranes, all filters utilized were disposable. The following filters were tested individually:

1. 5-Micron Filter--The function of this filter (manufactured by Filterite) is to prevent passage of particulate matter greater than 5 microns in diameter. The filter is integrally woven polypropylene and progressively removes particles from surface to core, i.e., by depth filtration. The filter medium is non-rupturing and generally has a large contaminant-holding capability.

2. Carbon Filter--A carbon filter was chosen to eliminate oxidizables (organic compounds). Two filters were investigated: (a) AMF Cuno containing 454 g of activated carbon and (b) Ecology, Inc., Seagull IV, a matrix of zeta plus media (a proprietary material that removes clays), powdered carbon and micro-screen.

3. Ion-Exchange--Removal of ions before the reverse osmosis membrane is important owing to concentration polarization, as discussed in Chapter II. The Millipore filter utilized was a mixed-bed strong-acid, strong-base exchanger.

4. Reverse Osmosis--Reverse osmosis (RO) filtration was chosen to be the main barrier for materials considered to be contaminants of USPXX water for injection. That is, RO has been shown to remove bacteria, viruses, pyrogens, organic and inorganic compounds.[57-59,63] The following RO membrane configurations (Figure 19) and compositions were utilized:

a. Spiral Wound

(1) Cellulose Triacetate--This is a common RO membrane material, manufactured by Millipore; it is utilized rather extensively.

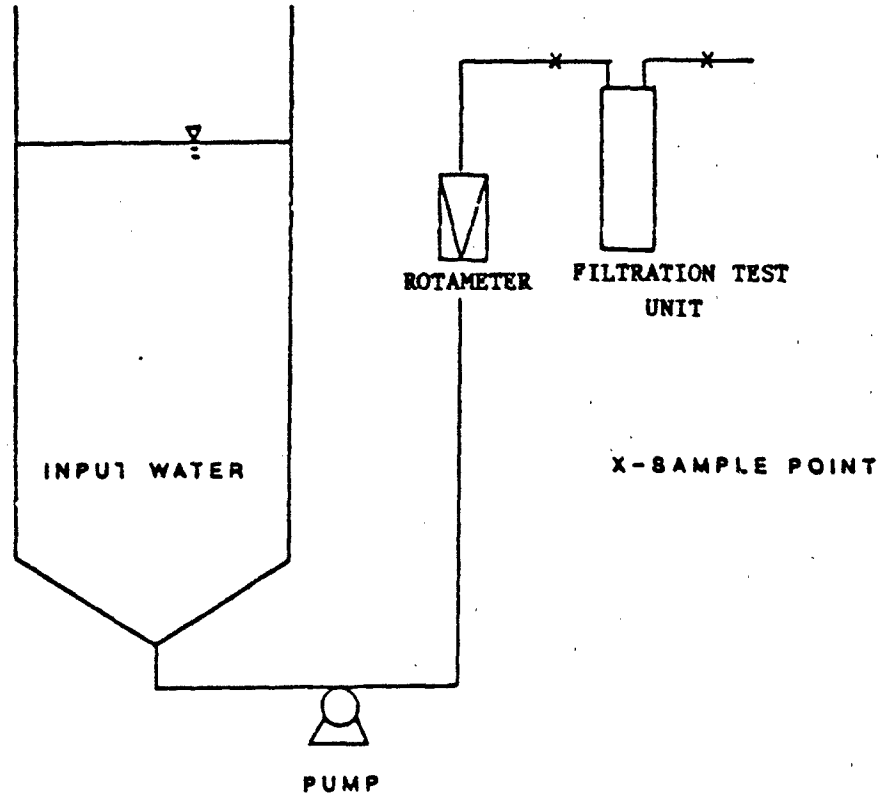


Figure 23. Schematic diagram of the test stand for evaluation of individual filtration methodologies.

(2) Thin-film Composite (Film-Tech)--A layering of low molecular weight polyethyleneimine (PEI) on a support such as polysulfone. The membrane "skin" is thinner than that made of cellulose triacetate and therefore the flux is generally greater (Equation 18).

b. Hollow Fiber--This inside-"skinned" RO (manufactured by Bend Research, Bend, OR) utilizes the RO fiber as the pressure vessel. The input water is pressurized in the lumen of the fiber and permeates to the outside wall. The fibers are composed of polyaromatic amides.

5. Teflon--Spiral wound filters made from teflon were obtained from Gore-Tex, Inc. The methodology utilized by this filter is analogous to distillation. The water is introduced at an elevated temperature and water vapor is transferred across the teflon membrane. After transfer of the vapor, condensation occurs on the effluent side of the membrane. This membrane is utilized for removal of organics, inorganics, and microbial populations.

6. Microfilter (Millipore)--A 0.22-micron millistack filter provides for bacterial occlusion. This filter was incorporated to assure bacterial sterility of the product water.

Sampling. Sampling was accomplished at each designated sample point, before and after each filter, including the sample water tank. A 1-liter wide-mouth ground-glass-stoppered pyrex bottle was utilized as the sample container.

The sample containers were depyrogenated (by lot) with dry heat at 250°C for at least 30 minutes as prescribed by the USP.[4] Depending upon the number of bottles per lot, at least one bottle was randomly selected and tested for pyrogens.

The bottle(s) were washed internally with 1 mL of USP WFI (obtained commercially from American McGaw). The rinse water was then tested for pyrogens with the LAL gel clot test (M.A. Bioproducts). In all cases, the LAL test was negative.

The sample points were composed of schedule 316 stainless steel tubing (3/8 inch) and Whitney 3/8 inch valves. The exceptions to the above were the RO reject and the product sample points, where samples were taken directly from the flow.

Analysis. The analytical methodology conformed to the USPXX, listed in Appendix B.

For pH measurements, an Orion model 811 pH meter was utilized with an Arthur H. Thomas, Inc., combination probe.

For determination of parameters delineated in USPXX, (Table 5), Nessler tubes with a comparison stand were utilized (Arthur H. Thomas, Inc., catalog number 3058). Initially in phase I, chloride, ammonia, sulfate, and calcium were determined by ion chromatography (Dionex Ion Chromatograph Model 16). As experimental runs progressed into phase II, the assay for chloride, ammonia, sulfate, and calcium were performed according to the methodology of USPXX (Appendix B). During both phase I and phase II, oxidizables, carbon dioxide, and heavy metals were determined as in USPXX.

TABLE 5. USP QUALITY STANDARDS FOR WFI

Test	Requirement
Pyrogen	Nonpyrogenic
Description	Passes (clear, colorless, odorless liquid)
Chloride	<0.5 ppm
Oxidizables	Negative
Total solids	0.022% for 1 L containers
Sulfate	Negative
Ammonia	<0.3 ppm
Calcium	Negative
Carbon dioxide	Negative
Heavy metals	Negative
pH	5.0–7.0

The total solids determination was as described in USPXX with the following variance: The evaporating dishes were heated in a muffle furnace, cooled in a desiccator and tared. The 100 mL sample was evaporated overnight in a Boekel drying oven at 105°C. The dishes were removed from the drying oven, cooled in a desiccator and weighed on a Mettler model H33. The weight of residue was calculated as in Standard Methods for Examination of Water and Wastewater.[109]

Initially, bacteriological determinations were conducted by means of serial dilutions and spread plating, thus yielding a quantitative determination. During phase two, microbial determinations were performed as indicated by the USPXX. The culture media utilized was USP Soybean-Casein Digest Medium and USP Fluid thioglycollate medium. Both media were commercially obtained from Oxoid, Inc., catalog numbers CM129 and CM391, respectively.

Viral assays, which are not required by the USP, were performed with LSc1 poliovirus. The poliovirus was harvested from infected HeLa cells and assayed with the HeLa cell line according to accepted protocol.[110] All viral samples were collected in separate sterile containers, with addition of 1 mL of Hank's balanced salt solution (HBSS) for each 9 mL of sample obtained. The HBSS ensures that the viral particles remain monodispersed. With the exception of the reverse osmosis permeate, all viral samples were serially diluted and assayed on a monolayer of HeLa cells with an agar overlay. After three days, the petri dishes were stained with neutral red and the number of plaques recorded.[110] For the reverse osmosis permeate, the samples were concentrated on a zeta-plus medium (1-MDS) and eluted as described by Sobsey.[111] The 1-MDS medium has an efficiency of 95 percent.[112]

Pyrogen testing was performed with the LAL purchased commercially from M.A. Bioproducts, Walkersville, MD (catalogue number 50-645U). With each set of samples, a positive control, a negative control, and an inhibition control were assayed. A sample of 0.1 mL was introduced to a vial of lysate, which was then placed in a heating block at 37°C for 1 hour. At the end of the time period, the vial was inverted to determine if the lysate had gelled (positive) or remained in the liquid state (which indicated a negative test).[75]

Phase II. Once the individual filter testing had been accomplished, a system was built, which is represented in Figure 24. The input water was potable water obtained from the Ft. Detrick water distribution system and dechlorinated with sodium thiosulfate as described in Standard Methods.[109]

The last experimental runs utilized water obtained from the Monocacy River, which drains Frederick County, MD.

RESULTS AND DISCUSSION

EFFICACY OF INDIVIDUAL FILTERS

The letter of agreement,[113] which enters this item into the Army's future inventory, specifies that potable water be utilized as the input water.[113] Therefore, a 750 gallon water tank was filled with Ft. Detrick tap water, which was dechlorinated with sodium thiosulfate as described in Standard Methods.[109] It was felt that the addition of ammonium chloride and ammonium sulfate (111 g/100 gallons) would ensure adequate challenge levels. To ascertain the efficacy of selected filters in removal of biologics, Escherichia coli and LSc1 poliovirus were added to the input water. An 18-hour culture of E. coli yielded a challenge of approximately 1×10^5 CFU/mL. The poliovirus was titered upon harvesting and an adequate amount was added to provide a challenge level of approximately 10^2 to 10^4 PFU/mL.

All other parameters tested (Table 5) under USPXX were indigenous to the potable water source. All filters with the exceptions of the reverse osmosis (RO), and Gore-Tex were rated at 5 gpm maximum flow. The millistack filter (0.22 µm), although rated at 5 gpm was capable of only 1.4 gpm maximum before the pressure reached the critical point for the filter container, i.e., 45 psi.

The cellulose triacetate RO unit was rated at 120 L/hour product or 0.528 gallons/minute. The input to this filter was 1.0 gallon/minute with 0.429 gallons/minute as the reject (brine) flow.

The thin film composite (TFC) RO unit was of double pass configuration, i.e., the reject from the second membrane was recycled to the input of the first module. The product flow from the TFC RO was 0.396 gallon/minute with the reject flow being 0.604 gallon/minute.

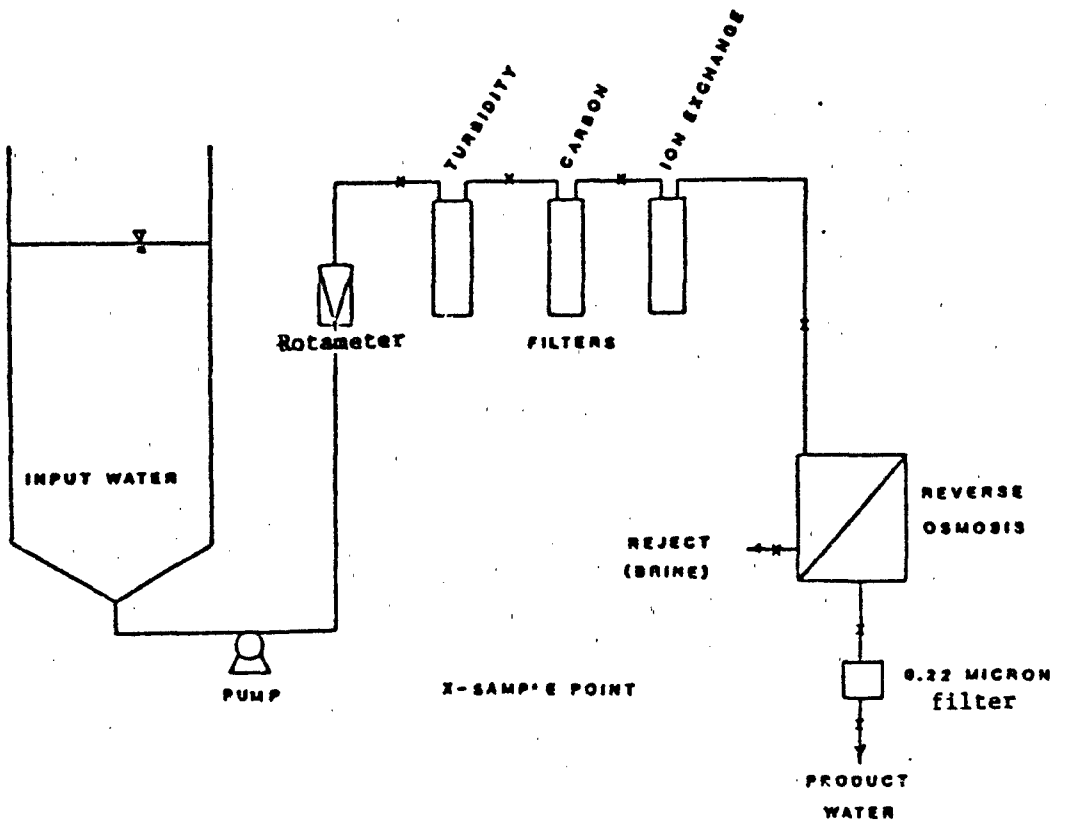


Figure 24. Schematic diagram of the treatment processes for producing USPXX water for injection.

Table 6 represents a performance summary of the chemical parameters with respect to influent for each filter. The filters summarized in Table 6 were not afforded any form of pretreatment. This was done to ascertain the individual filter responses.

As may be determined from Table 6, the most effective filtration treatment for removal of lipopolysaccharides (endotoxin) was the RO membrane. However, other treatment methodologies must be utilized in conjunction to condition the water before the RO membrane since, in this series of tests, salt removal was inconsistent. (Due to the standards of TB MED 229, field treated water will not be considered potable if heavy metals are present.[114] Therefore, heavy metals were omitted as an input parameter.)

Coliform and viral removal were also investigated in considerable detail.

Figures 25 through 31 (pages 64-70), represent the colony forming units per mL (CFU/mL) of E. coli. The axis labeled input represents the load of E. coli introduced to the influent side of the filter from the seed tank (750 gallon tank). The geometric means were calculated (log-normal distribution) as were the standard errors of the mean, which were also plotted. The geometric means were back-transformed and plotted on a semi-logarithmic scale.

Figure 25 represents the efficacy of the 5 micron spun-woven filter in removal of E. coli. The results, which show no reduction, were not unexpected since the filter was rated as 5 micron nominal. Escherichia coli has been reported to be approximately 0.4 to 0.7 microns in width by 1 to 4 microns in length.[115]

The filtration effect of the carbon filter (AMF Cuno) is reported in Figure 26. A reduction of approximately one-half an order of magnitude is seen from the input levels at a 2-gallon per minute flow.

Figure 27 represents the effect of the Everpure water softener filter on E. coli. The maximum reduction is again one-half an order of magnitude, but at 3 gallon/minute.

Figure 28 represents the effect of the strong-base, strong-acid, mixed-bed ion exchange filter (Millipore). This filter approaches an order of magnitude reduction for the input E. coli at 2 gallon/minute.

Figure 29 represents the effect of the cellulose triacetate single-pass reverse osmosis (Millipore) filter. As indicated by the graph, the 1-gallon per minute (gpm) input yielded a 5-log reduction in E. coli from input to permeate side of the membrane. The 2-gallon per minute input yielded somewhat less reduction than the 1 gpm (the rated flow).

Figure 30 represents the most dramatic reduction of E. coli, which was as expected. The 0.22 micron filter is extremely effective in microbial occlusion. As indicated, no bacterial colonies were present upon membrane analysis utilizing a 100 mL sample volume of the effluent. The 0.22 micron filter yielded more than an 8 log reduction.

TABLE 6. RESULTS OF INDIVIDUAL FILTER TESTS

	5 Micron	Cuno Carbon	Water Softener	Ion[a] Exch	CA RO	TFC RO	0.22 μ	Seagull IV	Gore-Tex	Bend RO
LAL	0/3[b]	0/3	0/3	0/3	3/3	3/3	0/3	0/3	2/3	0/3[c]
CO_2	0/3	0/3	1/3	1/3	3/3	1/1	0/2	2/3	1/1	—
Heavy Metals	3/0	3/0	3/0	3/0	3/0	3/0	3/0	3/0	3/0	—
Oxid	0/3	0/3	0/3	0/3	1/3	3/3	0/3	1/3	3/3	—
Cl	0/2	0/2	0/3	1/2	0/3	2/3	0/2	0/3	3/3	—
SO_4	0/2	0/2	0/3	1/2	0/3	2/3	0/2	0/3	2/3	—
Ca	0/3	0/3	0/3	1/3	3/3	3/3	0/3	0/3	3/3	—
NH_3	0/2	0/2	1/3	1/3	0/3	2/3	0/3	0/3	0/2	—
TDS	0/3	0/3	0/3	0/3	0/3	2/3	0/3	0/3	3/3	—

a. The ion exchange was successful in reducing the calcium levels, although not to the level of the stringent USPXX requirements.
b. The left hand number represents the samples that were within USPXX WFI requirements. The right hand number indicates the number of positive samples input to the filter in question.
c. The Bend hollow fiber RO continually yielded a positive LAL after several days of continual operation, therefore it was dropped from the protocol.

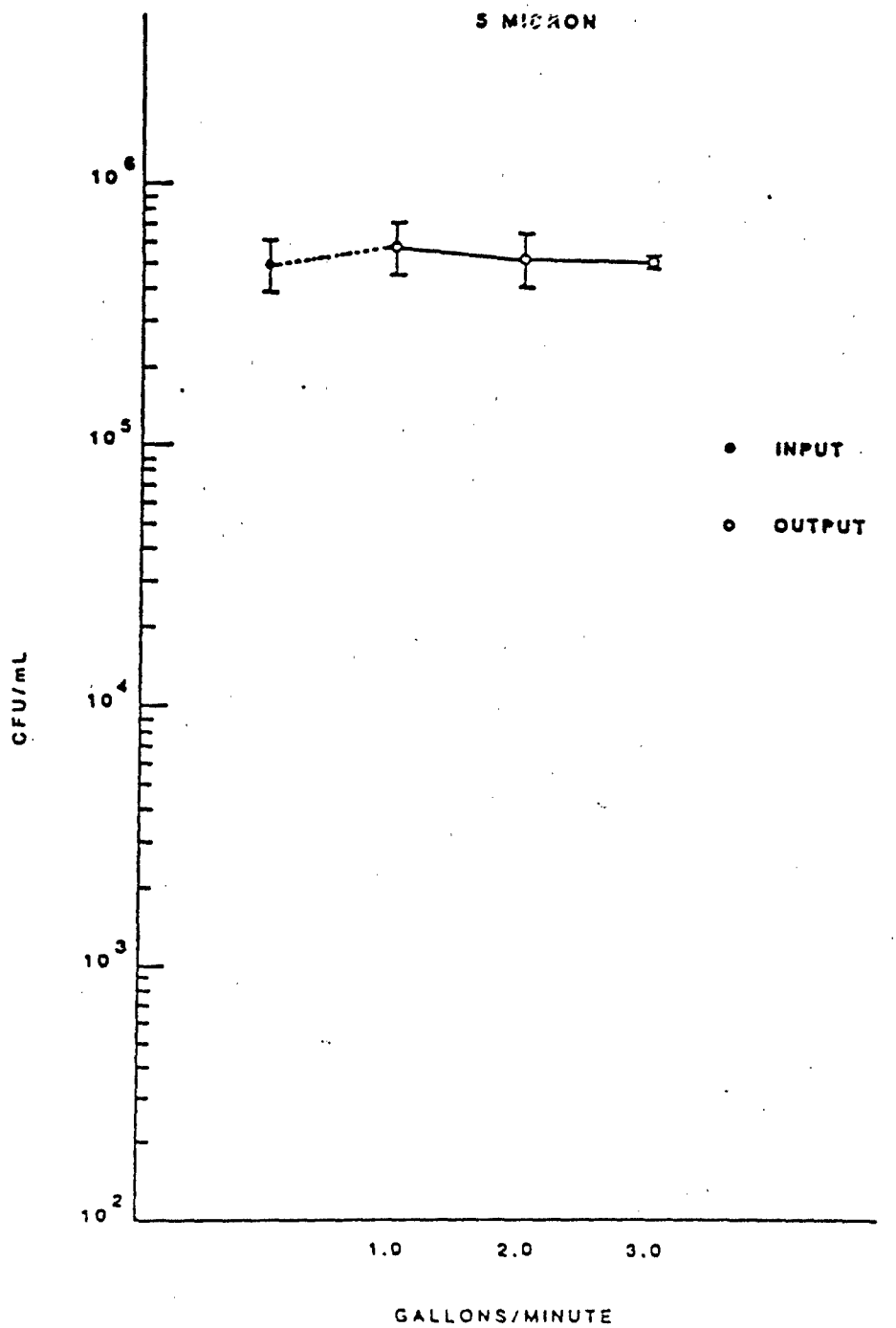


Figure 25. The occlusion of E. coli to the 5 micron spun-woven filter. The bars represent ± 1 standard error of the mean.

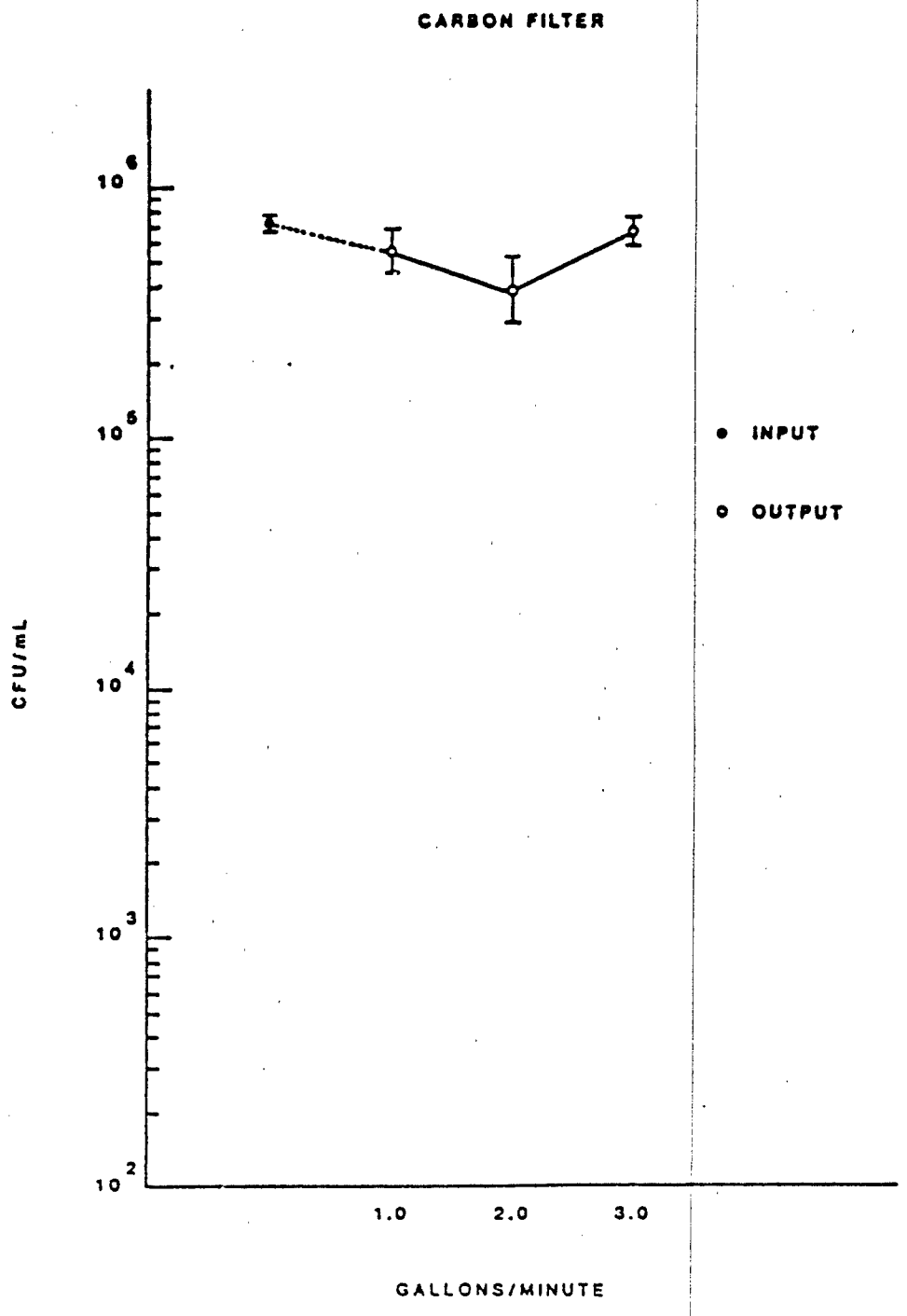


Figure 26. The occlusion of E. coli to the carbon filter. The bars represent ± 1 standard error of the mean.

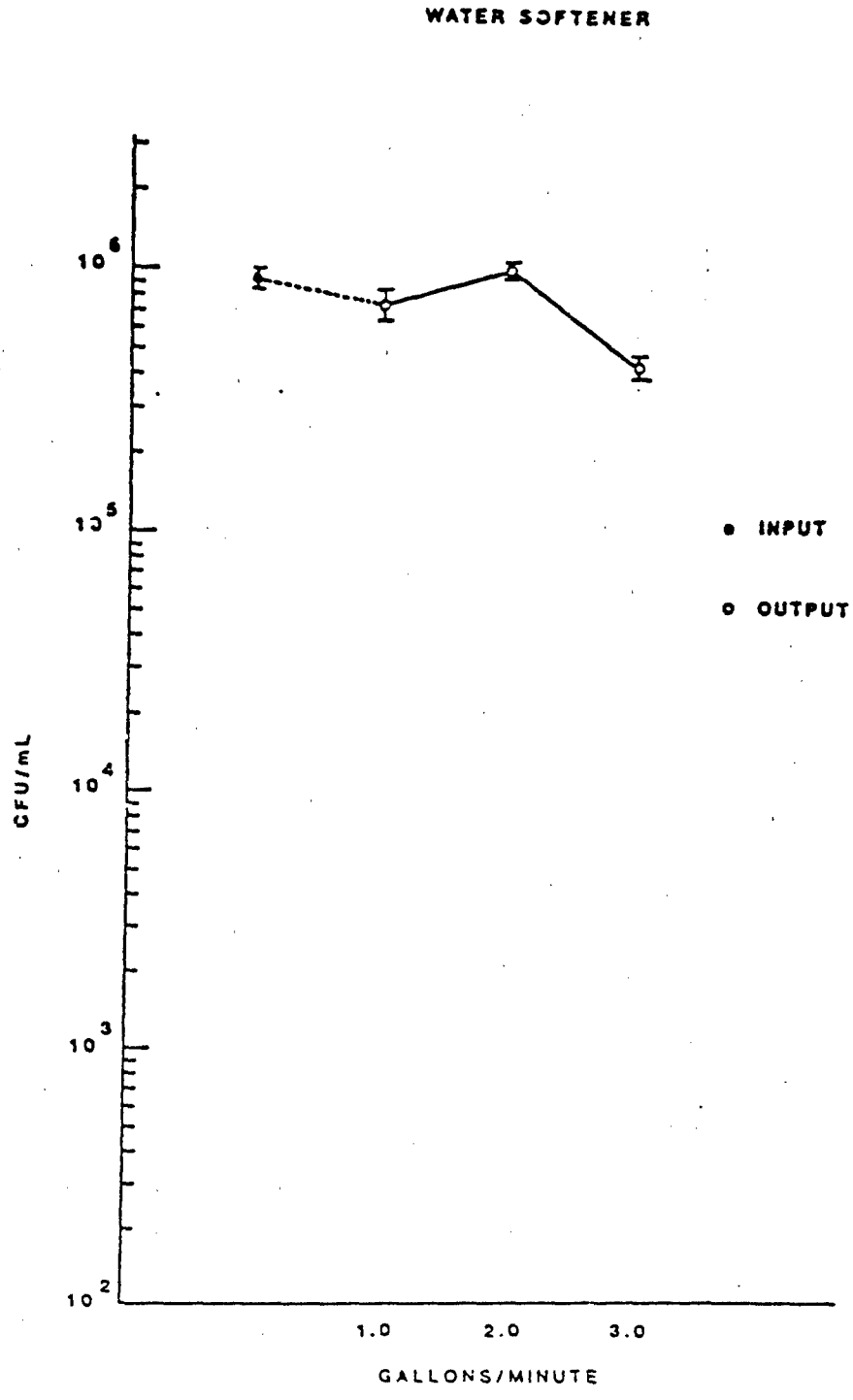


Figure 27. The occlusion of E. coli to the water softener filter. The bars represent ± 1 standard error of the mean.

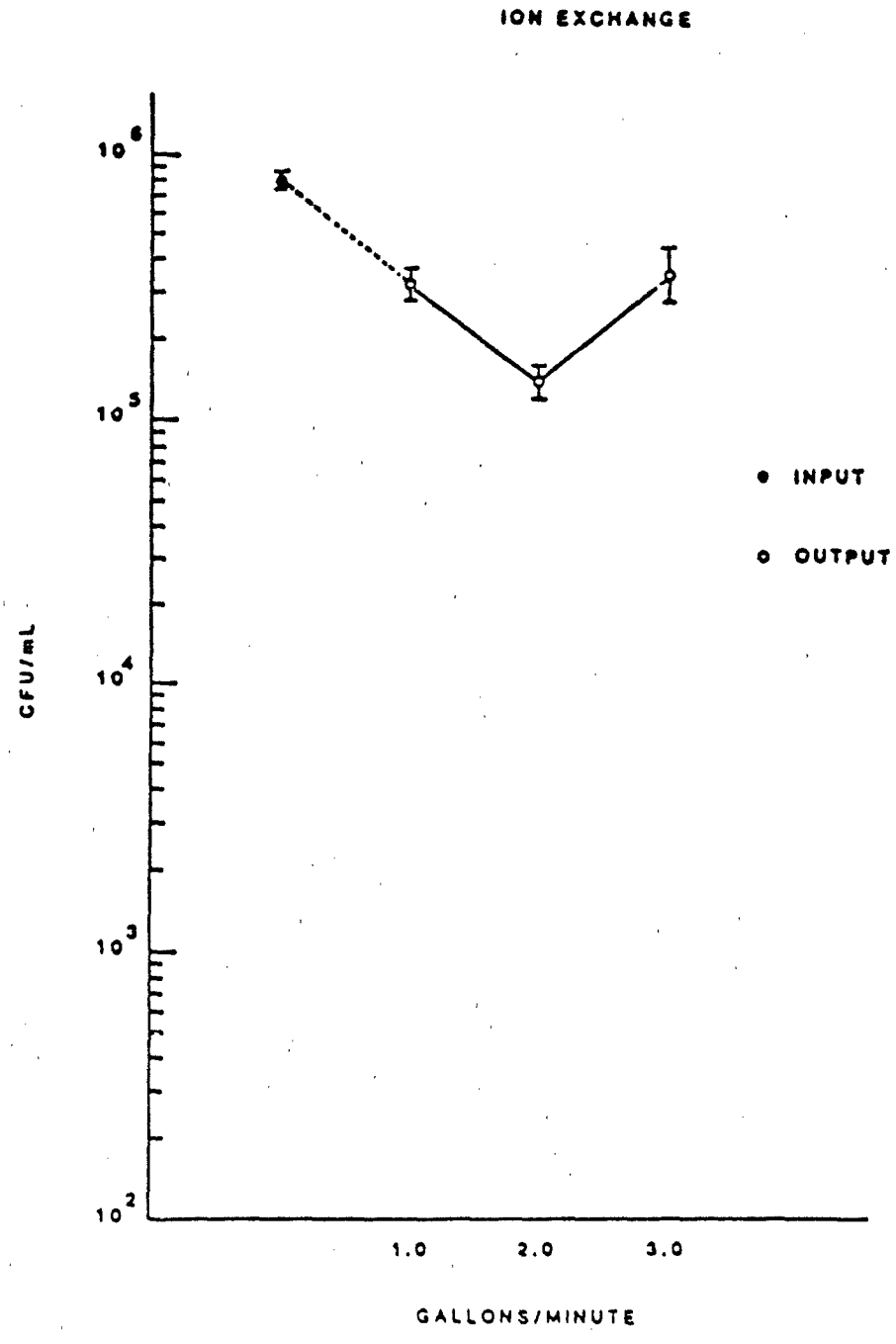


Figure 28. The occlusion of E. coli to the ion exchange filter. The bars represent ± 1 standard error of the mean.

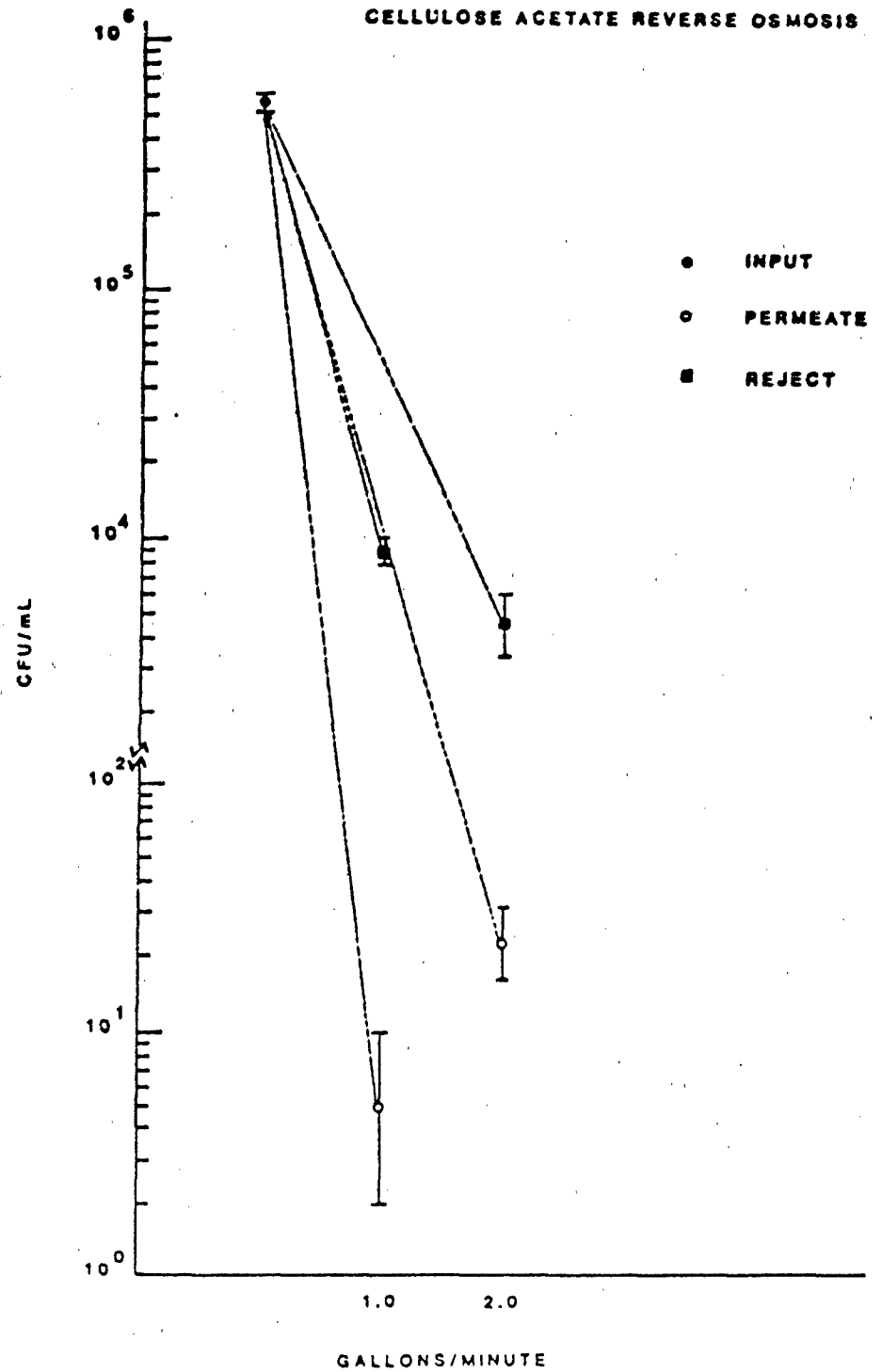


Figure 29. The occlusion of E. coli to the cellulose triacetate reverse osmosis membrane. The bars represent ± 1 standard error of the mean.

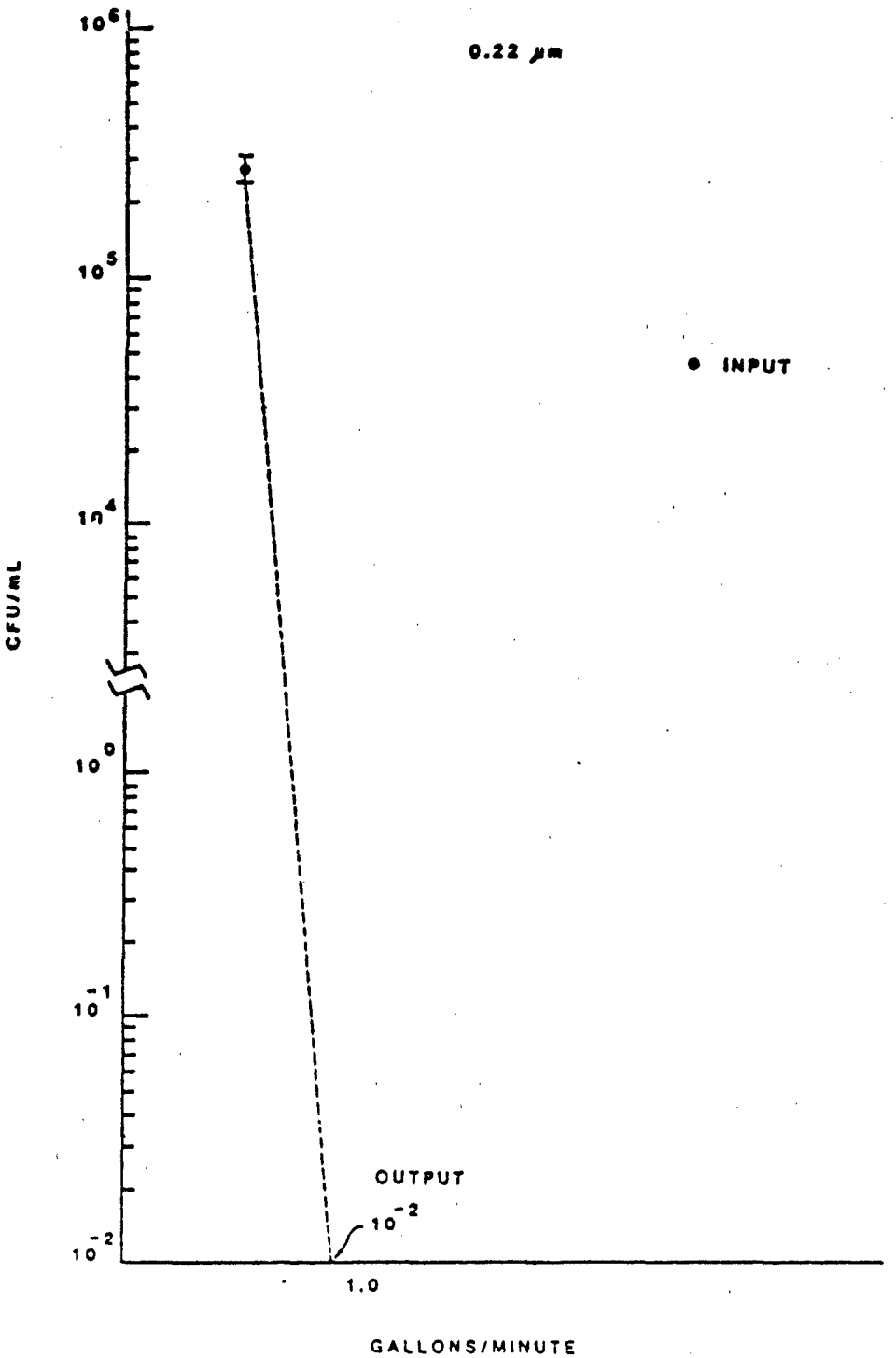


Figure 30. The occlusion of E. coli to the 0.22 micrometer filter. The bars represent ± 1 standard error of the mean.

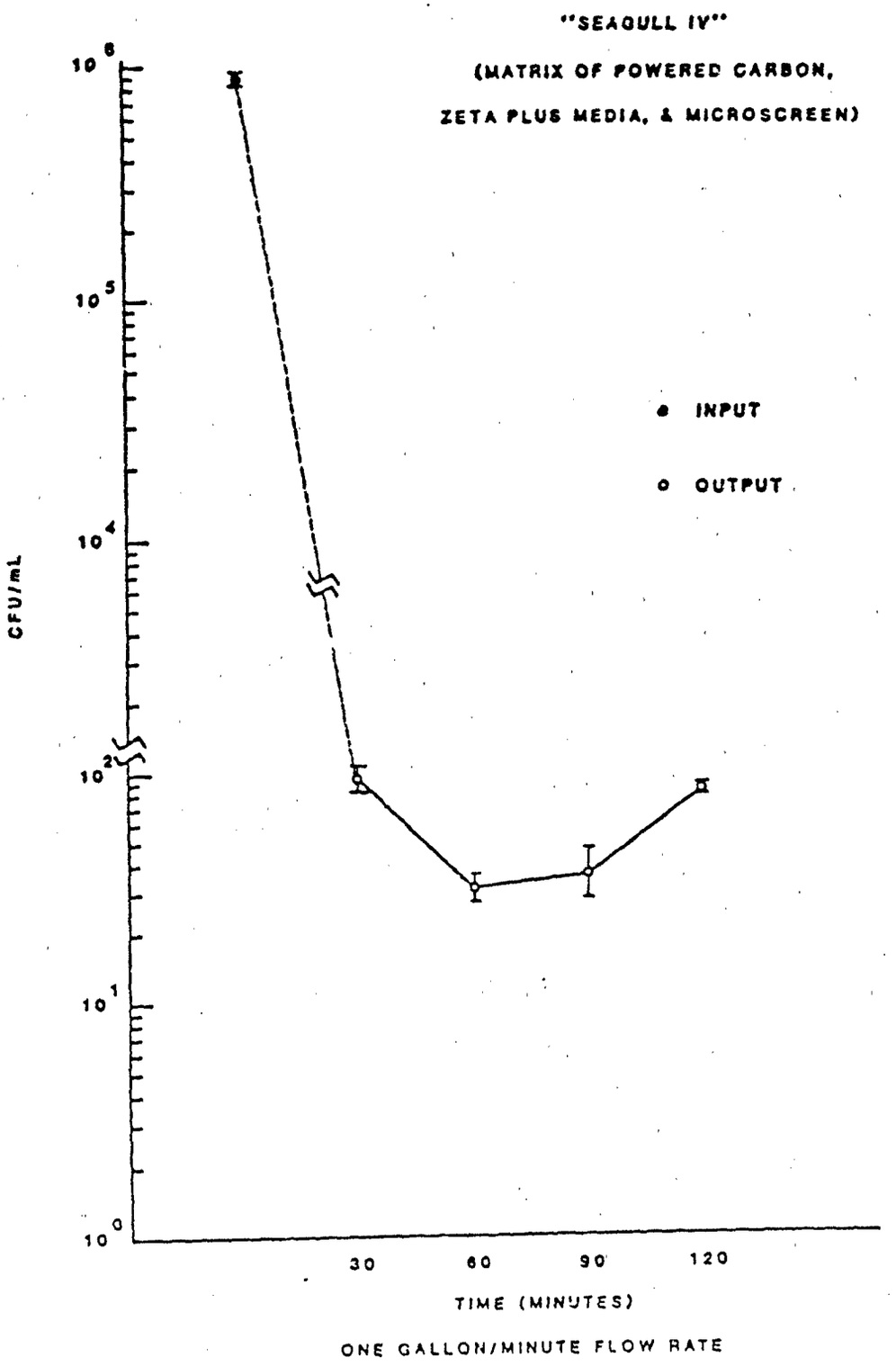


Figure 31. The occlusion of E. coli to the "Seagull IV" filter. The bars represent ± 1 standard error of the mean.

The last filter to be tested against E. coli was a commercial filter by Ecology, Inc. termed Seagull IV. The filter was rated at 2 gallons per minute but since the RO was most efficient at 1 gallon per minute the Seagull filter was tested at that flow rate. The Seagull filter is composed of powdered activated carbon, zeta plus matrix and microscreening. The filter materials are combined in a proprietary formula.

Table 7 lists the percent reduction of E. coli over the test. As Figure 31 indicates, the greatest reduction occurs over the first 60 to 90 minutes.

TABLE 7. REDUCTION OF ESCHERICHIA COLI WITH THE "SEAGULL IV" CARBON FILTER

Time, min	Percent Reduction from Input
30	99.989
60	99.996
90	99.996
120	99.991

The filters that demonstrated one log reduction or less are obviously not suitable or intended for use as microbial occlusion filters. Therefore, the prime filtration methodologies to be relied upon for bacterial occlusion are the RO and the 0.22 micron filters.

The next set of figures, 32 through 40 (pages 72-80), represents the effect of the various filtration media on LSc1 poliovirus, as expressed in plaque forming units (PFU).

Figure 32 represents the 5 micron filter. The results are as expected, i.e., there is no effect by the filter on viral population.

Figure 33 represents the effect of a carbon filter (AMF Cuno) on virus filtration. The most dramatic effect occurs at the 1-gallon per minute flow rate, which yielded a reduction of 95.5 percent.

Figure 34 represents the Seagull filter (Ecology, Inc.). Viral reduction is most dramatic and in all probability due to the zeta plus matrix in the filter composition and the overall electronegativity of the charged viral particle. The reduction of over 9 logs represents remarkable efficiency.

Figure 35 represents the effect of the water softener (Everpure, Inc.) on viral occlusion. No significant reduction was achieved with this filter.

Figure 36 indicates that ion-exchange also had no effect upon virus removal. (The bars representing ± one standard error of the mean are

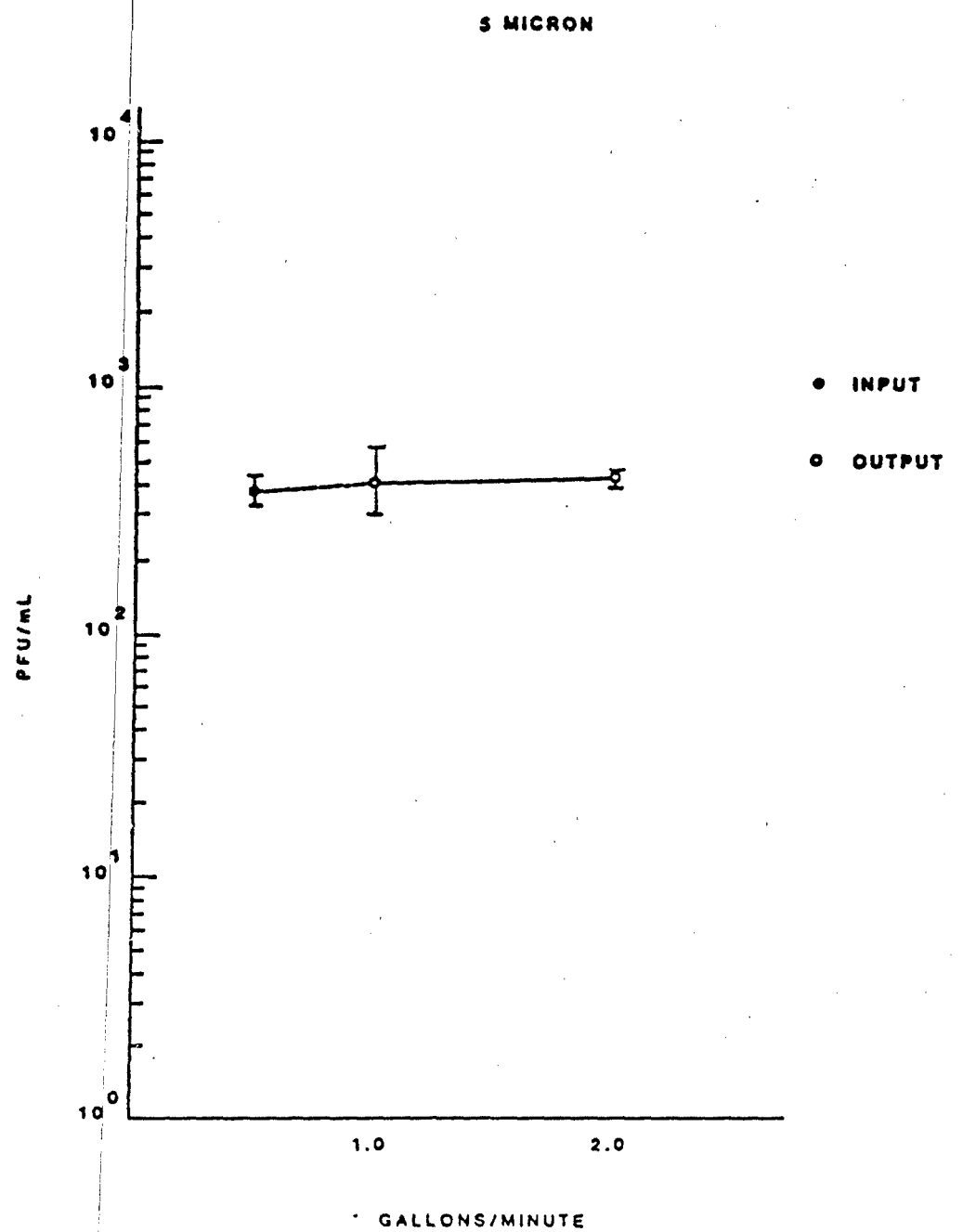


Figure 32. The occlusion of LSc1 poliovirus to the 5 micron spun-woven filter. The bars represent ± 1 standard error of the mean.

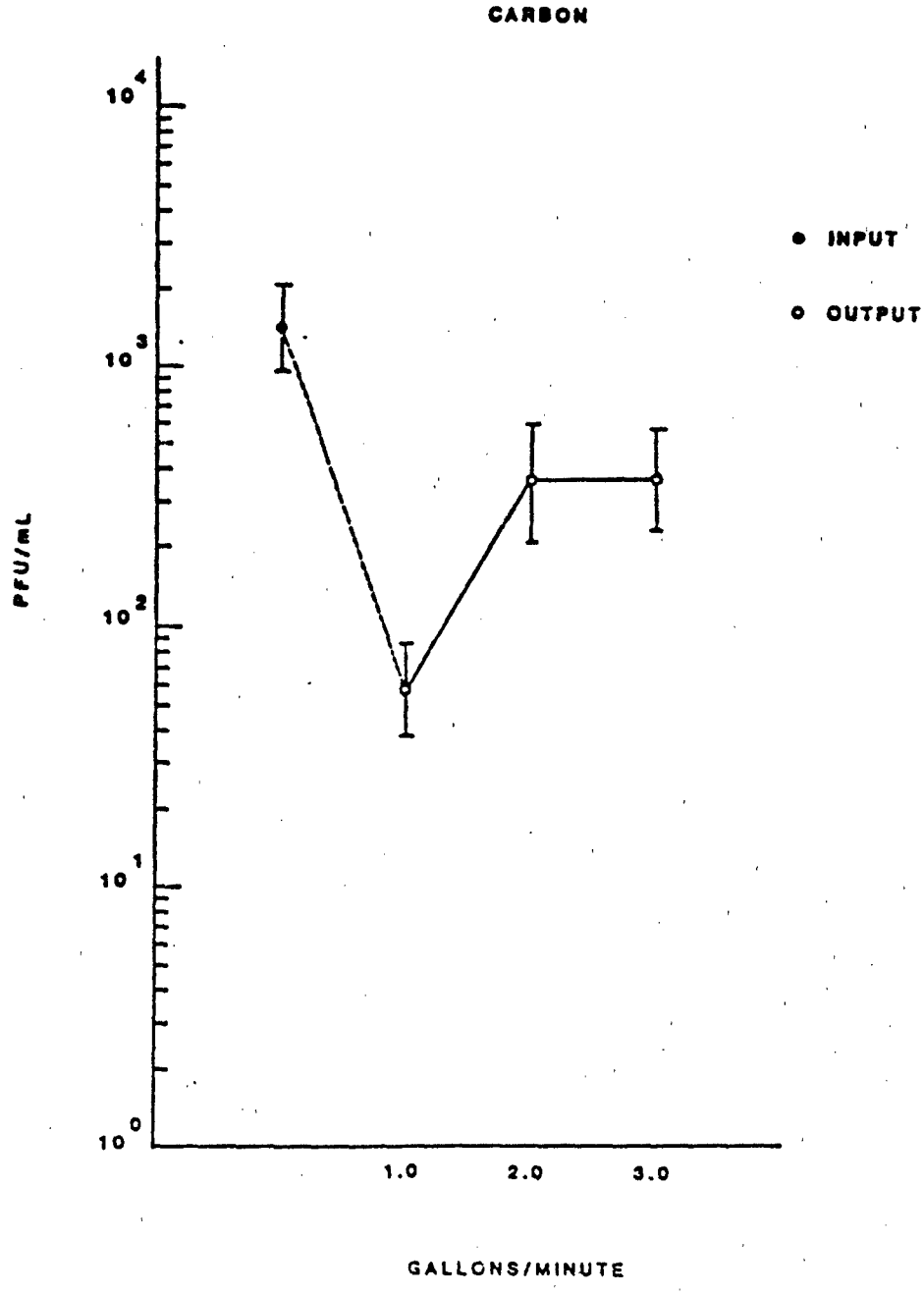


Figure 33. The occlusion of LSc1 poliovirus to the AMF Cuno carbon filter. The bars represent ± standard error of the mean.

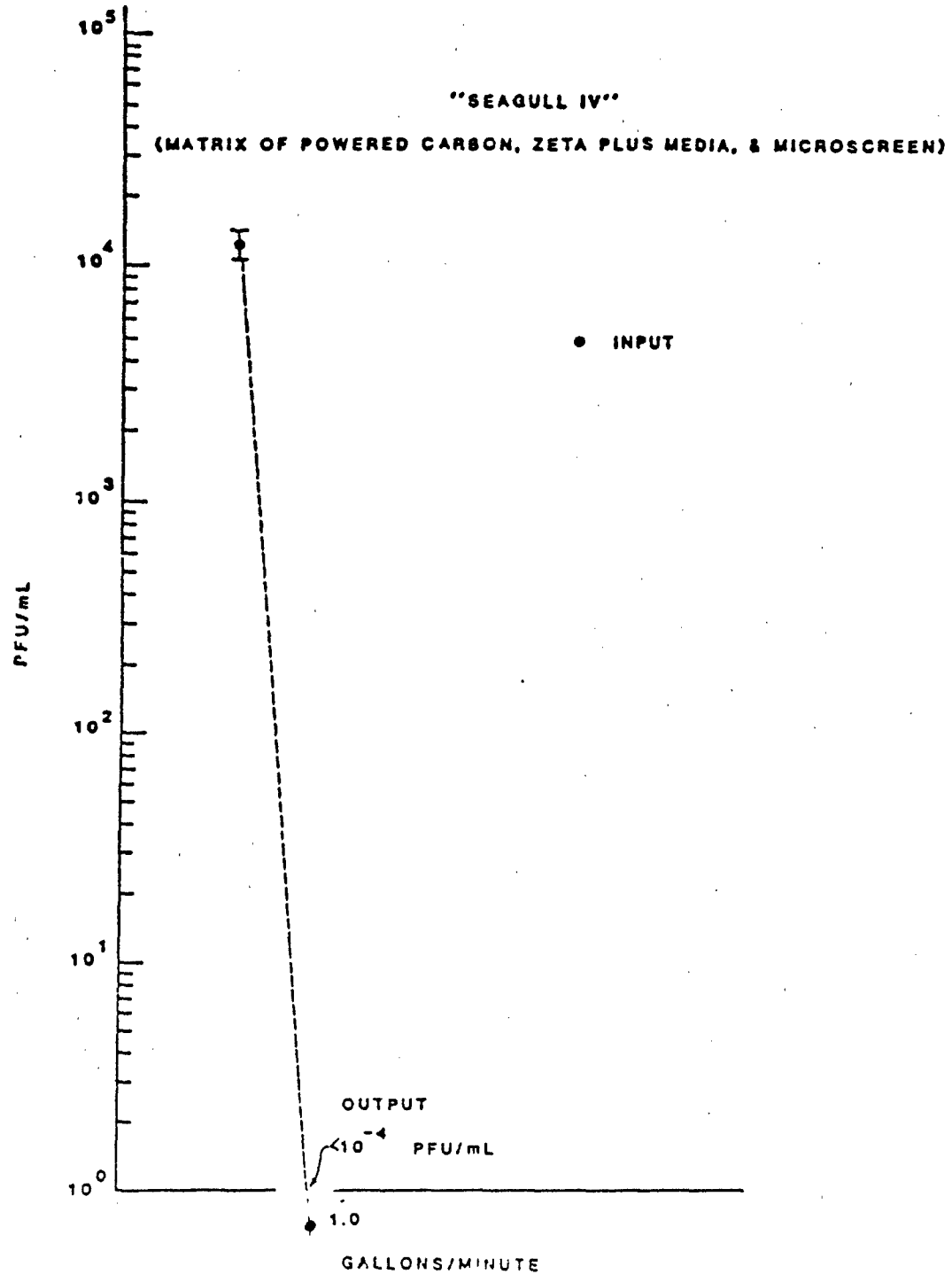


Figure 34. The occlusion of LSc1 poliovirus to the "Seagull IV" carbon filter. The bars represent ± standard error of the mean.

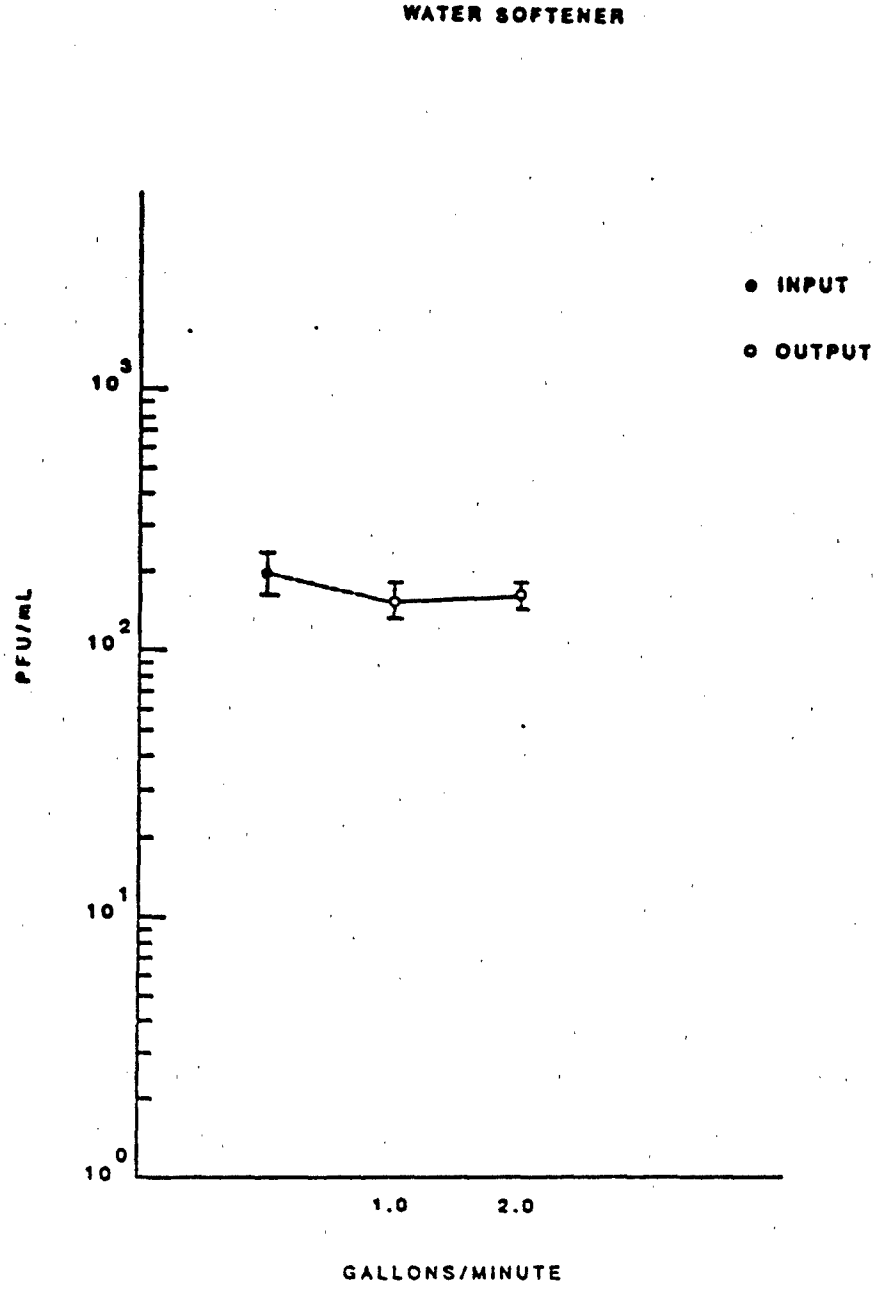


Figure 35. The occlusion of LSc1 poliovirus to the water softener. The bars represent ± 1 standard error of the mean.

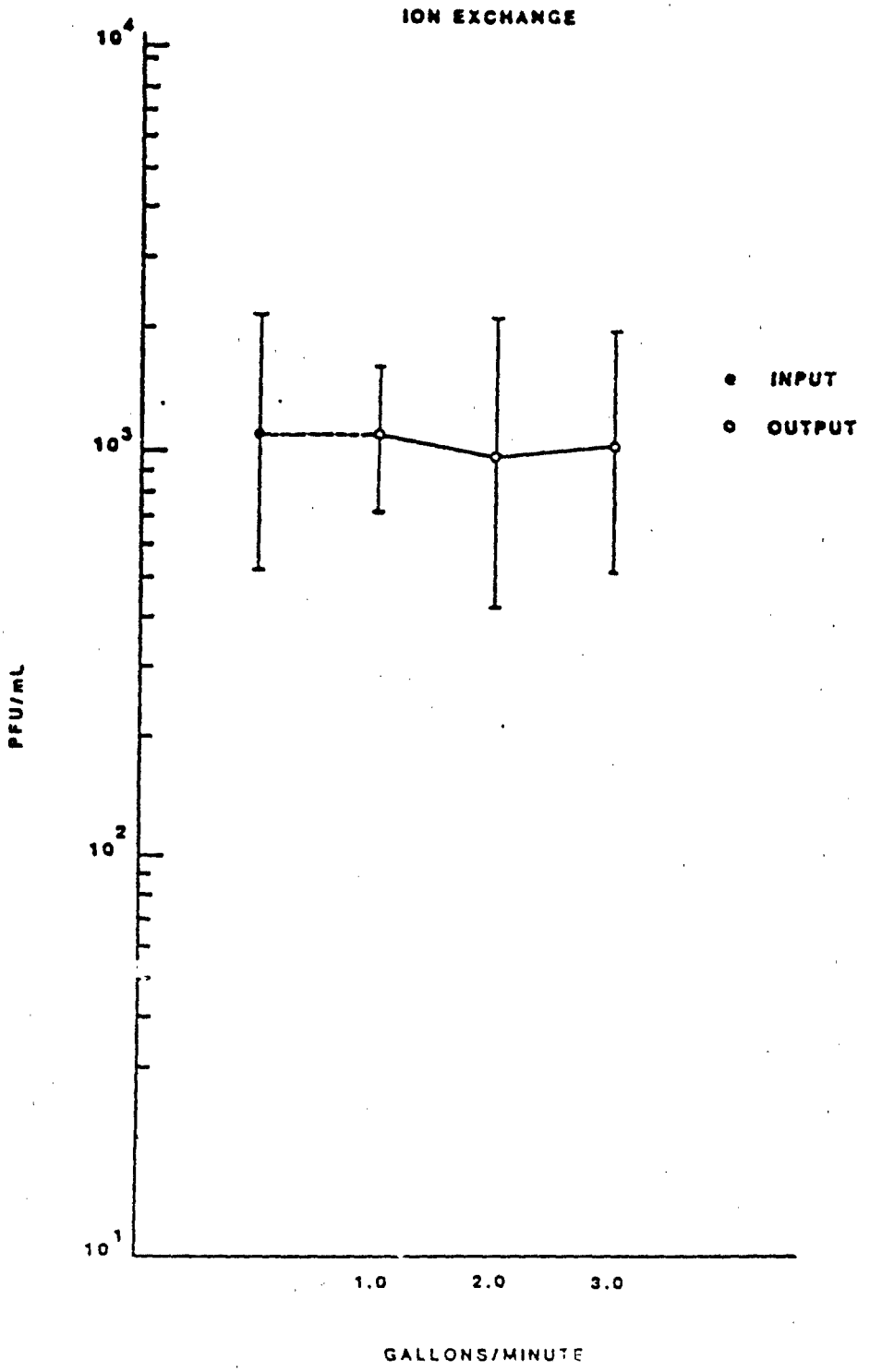


Figure 36. The occlusion of LScl poliovirus to the ion exchange filter. The bars represent ± 1 standard error of the mean.

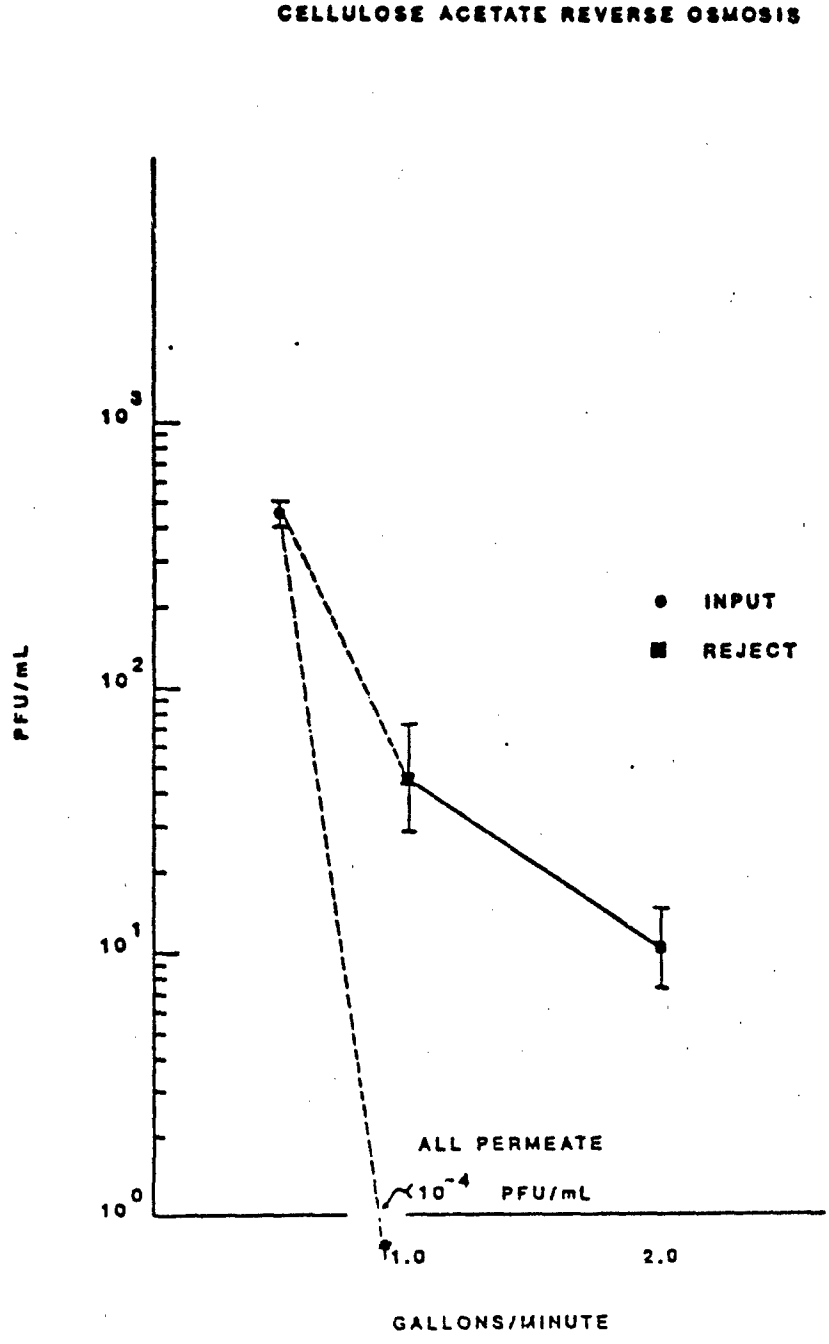


Figure 37. The occlusion of LScl poliovirus to the cellulose triacetate reverse osmosis membrane. The bars represent ± 1 standard error of the mean.

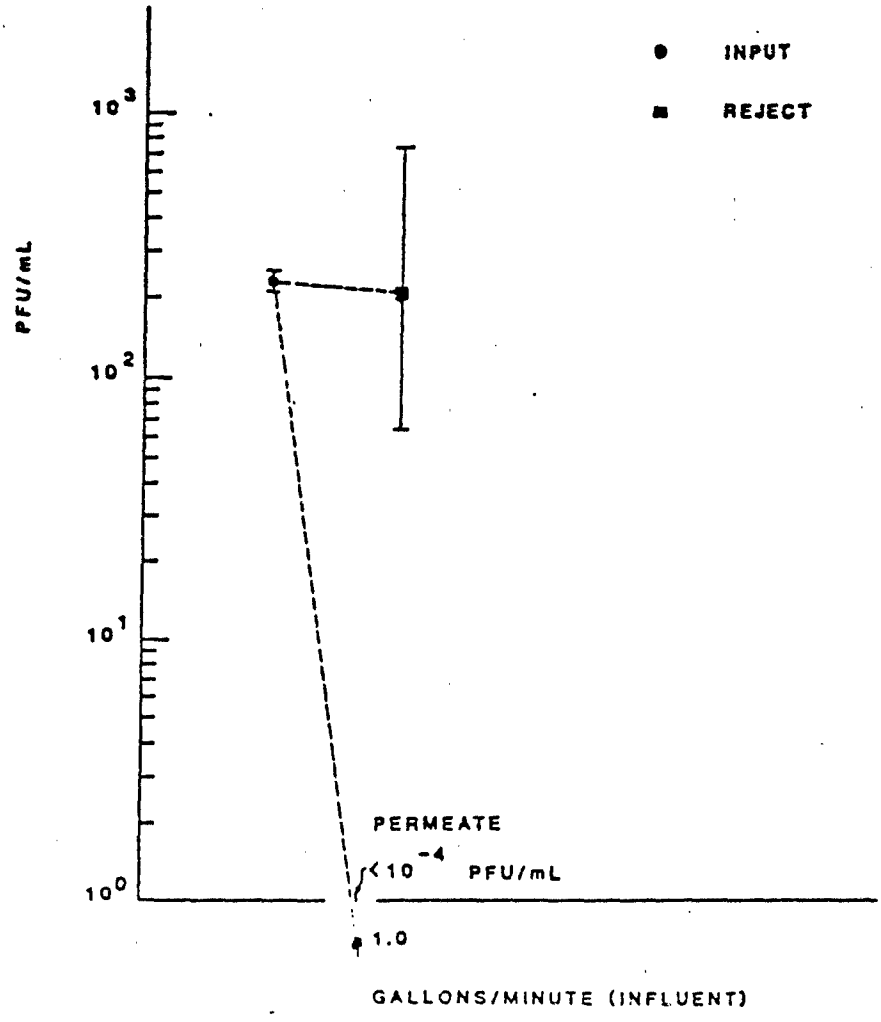


Figure 38. The occlusion of LSc1 poliovirus to thin-film composite reverse osmosis membrane. The bars represent ± 1 standard error of the mean.

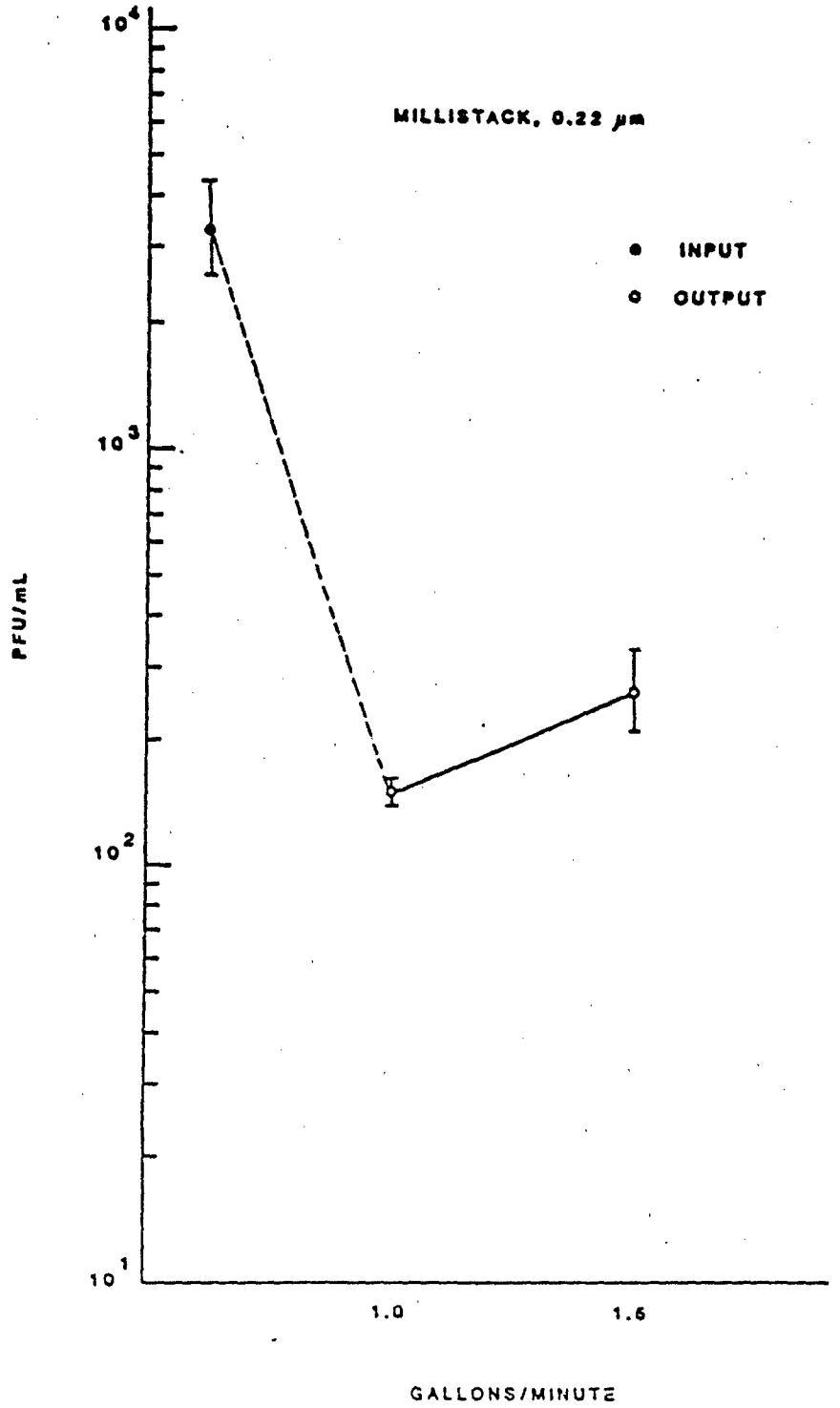


Figure 39. The occlusion of LScl poliovirus to the 0.22 micrometer filter. The bars represent ± 1 standard error of the mean.

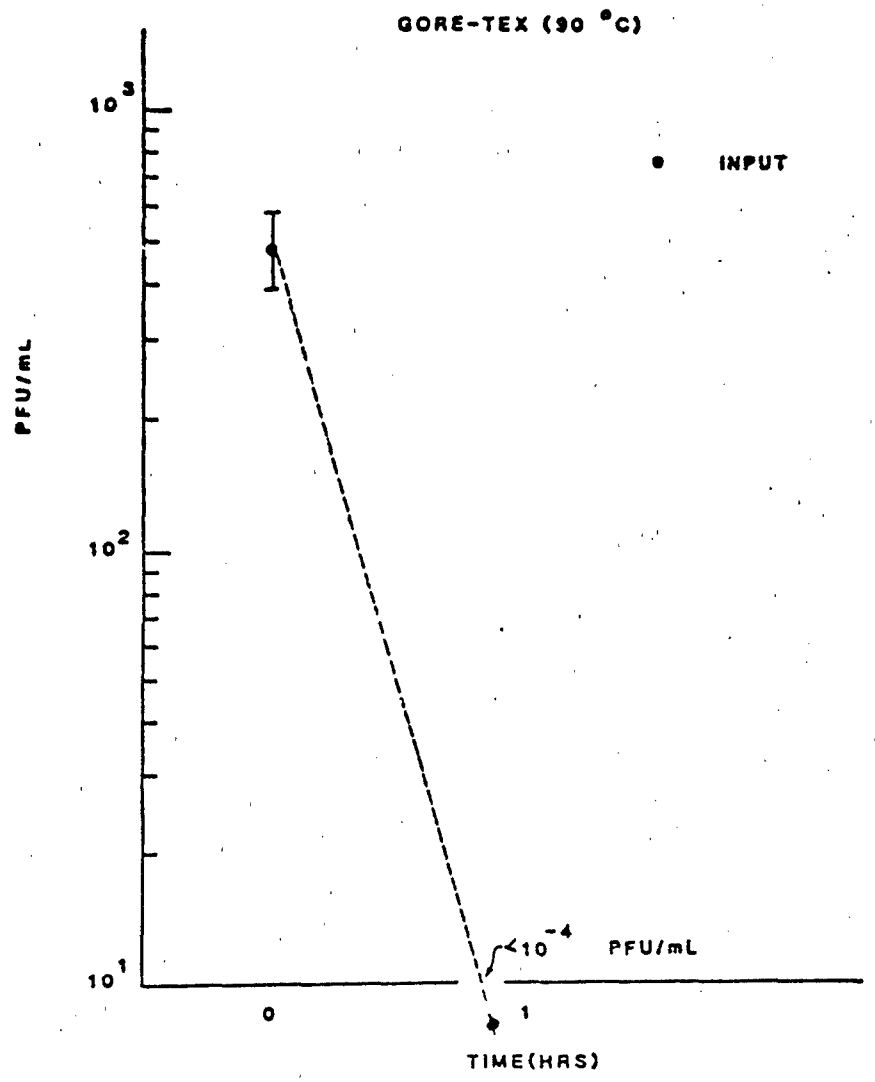


Figure 40. The occlusion of LScl poliovirus to the "Gore-Tex" filtration system. The bars represent ± 1 standard error of the mean.

abnormally spread away from the mean due to a problem with the HeLa cell line during the testing period.)

Figures 37 and 38 represent the cellulose triacetate RO (Millipore) and the thin-film composite (Film-Tech) double pass filters. The viral occlusion of both systems is rather dramatic, i.e., over seven orders of magnitude.

Figure 39 indicates the effect of the 0.22 micron (Millipore) filter with respect to viral occlusion. At 1 gallon per minute, reduction of approximately one and a half orders of magnitude was realized. To attain the flow rate of 1.5 gallons per minute, the pressure was increased to the maximum allowable for the filter housing, i.e., 45 psi. Although the 0.22 micron filter utilizes a tortuous path, the increase in pressure was sufficient to increase the number of viral particles exiting the filter.

Figure 40 represents the Gore-Tex module tested at USAMBRDL. No viral particles were found on the condensate side of the teflon membrane. This was due to the run temperature of 90°C, which would inactivate polioviruses.

The following discussion pertains to the treatment train of the unit settled upon for producing USPXX WFI. Figure 24 is a schematic of the basic treatment train.

The Seagull filter was brought to the forefront well after the system runs began utilizing the single pass RO with the AMF Cuno carbon filter.

The water softener filter was removed from the treatment train due to the increase in TDS by the resin exchange of two sodium ions for each divalent cation removed.

EFFICACY OF THE TREATMENT SYSTEM UTILIZING POTABLE WATER

Tables 8 and 9 represent the data obtained during the system runs for both the cellulose acetate and the thin-film composite RO membranes.

TABLE 8. SINGLE PASS (CELLULOSE ACETATE) REVERSE OSMOSIS SYSTEM[a]

Filter	LAL	CO_2	OXID	Ca^{++}	CL^-	$SO_4^=$	NH_3	TDS	pH
Turbidity	0/12	0/12	0/12	0/9	0/12	0/12	0/12	0/12	12/12
Carbon	0/12	0/12	0/12	0/9	0/12	0/12	0/12	0/12	10/12
Ion Exch	0/12	0/12	0/12	0/9	0/12	0/12	0/12	0/12	10/12
RO	8/12	6/12	12/12	12/12	0/12	12/12	0/12	0/12	11/12

a. The left hand number represents the samples that were within USPXX WFI requirements. The right hand number indicates the number of positive samples input to the filter in question.

TABLE 9. DOUBLE PASS (THIN FILM COMPOSITE) REVERSE OSMOSIS SYSTEM[a]

Filter	LAL	CO_2	OXID	Ca^{++}	CL^-	$SO_4^=$	NH_3	TDS	pH
Turbidity	0/10	2/10	0/10	0/10	0/10	0/10	5/10	0/10	5/10
Carbon	0/10	2/10	0/10	0/10	0/10	0/10	5/10	0/7	5/10
Ion Exch	0/10	3/10	0/10	1/10	0/10	0/10	5/10	0/7	5/10
RO	7/10	9/10	10/10	10/10	5/10	10/10	5/10	6/7	8/10

a. The left hand number represents the samples that were within USPXX WFI requirements. The right hand number indicates the number of positive samples input to the filter in question.

Table 10 is the percent reduction of ammonia across the cellulose acetate and the thin-film composite RO membranes (potable water supplies that have been chlorinated to TB MED 229 standards, i.e., to 10 ppm FAC after a 30 minute contact time, would not be expected to contain appreciable amounts of ammonia).

TABLE 10. PERCENT AMMONIA REDUCTIONS

Cellulose acetate	82.7
Thin-film composite	94.5

Table 11 relates the percent TDS reduction and challenge level for the two species of RO membrane. Although the input TDS levels to the RC membranes differed by 137 mg/L, the cellulose acetate membrane would have been out of the required range if it had been challenged with 589 mg/L. That is, an 89 percent reduction rate would have given approximately 64.8 mg/L TDS which is 44.8 mg/L above the limit set by USPXX. Conversely, had the thin-film composite RO membrane been challenged with 726 mg/L TDS, it would have yielded 14.5 mg/L which is 5.5 mg/L less than the requirements of USPXX. Neither, of course, would achieve the USP standard if challenged at 1,500 mg/L, the maximum under TB MED 229. For this reason, supplemental treatment for TDS must be considered.

TABLE 11. TOTAL DISSOLVED SOLIDS REDUCTIONS

	Reduction Percent	Challenge Level mg/L
Cellulose acetate	89	726
Thin-film composite	98	589

Table 12 indicates the percent reductions of E. coli across the treatment train at the indicated challenge level. The greatest reduction occurs across the RO membranes and the 0.22 micron filter, as expected.

TABLE 12. MICROBIAL REDUCTIONS
(Challenge Level 10^5 CFU/mL)

Turbidity filter	0
Carbon	22%
Ion exchange	60%
Cellulose acetate	99.999%
Thin-film composite	99.999%
0.22 µm	>7 log reduction

Because of the viral assays reported previously, and the resources required to perform assays, additional viral removals were not measured. The RO membrane has consistently given no detectable plaque from 500 mL sample concentrates and it was not deemed necessary to continue the assays.

Tables 8 and 9 are somewhat misleading if not viewed in light of the stringent requirements of USPXX (Table 5).

The lower limit of the calcium test in USPXX was determined to be less than 2 mg/L. Therefore, although the ion exchange filter was reducing the calcium concentration, it was not reducing it enough to yield a negative test by USPXX standards (Table 13).

However, the main function of the ion-exchange filter in this system is to reduce the divalent ions to a concentration of a few parts per million to prevent concentration polarization on the membrane surface. By keeping the concentration polarization to a minimum at all times and with the concomitant fluid management techniques employed by RO manufacturers, the problem of solute "breakthrough" will be minimized.

TABLE 13. CALCIUM ACROSS THE ION EXCHANGER

Mean Input (mg/L)	Mean Output (mg/L)	% Reduction
31.9	5.2	83.7

EFFICACY OF THE TREATMENT SYSTEM UTILIZING MONOCACY RIVER WATER

The final experiment was to determine whether the treatment train consisting of a 5 micron turbidity filter, Seagull IV carbon filter, ion exchange, thin-film composite RO, and 0.22 micron filter would produce USPXX WFI from a river source.

Water was obtained from the Monocacy River near Frederick, MD. Table 14 delineates the potable field water standards from TB MED 229.[114]

Table 15 represents the input water at ambient pH of 8.04. Table 16 represents a sample of Monocacy River water in which the pH was adjusted to 7.31 with carbon dioxide.

In Table 15, during the AM run, USPXX WFI production failed due only to the TDS value of 92 mg/L from the RO and 82 mg/L from the 0.22 micron filter. An explanation of the TDS in the AM sample is that the concentration polarization built to a level that the diffusivity force drove solute through the membrane. The other TDS samples (Tables 15 and 16) were taken when this effect did not occur.

As noted in Table 15, bacteria were present in the RO permeate for all runs but not after the 0.22 micron filter.

Table 16 indicates a positive sample for bacteria after the 0.22 micron filter. This is due to operator error. The 0.22 micron has proven to successfully occlude bacteria.

The USPXX sterility test consists of adding a sample (1 or 2 mL) to a sterile tube of Tryptic Soy Broth and incubating the tube for 14 days at 37°C. If even one bacterial cell were to be introduced to the medium, the test would be positive at the end of a 14-day incubation period. This points to the necessity of a 0.22 micron filter for bacteriological quality assurance.

TABLE 14. POTABLE WATER STANDARDS FOR FIELD SUPPLIES[a]

Constituent	Standard
Physical	
Color	50 platinum-cobalt units
Odor	—
Turbidity	5 Jackson units
Chemical	
Ammonia	—
Arsenic	0.2 mg/L
Carbon dioxide	—
Calcium	—
Chloride	600 mg/L
Cyanide	2 mg/L
Magnesium	150 mg/L
Oxidizables	—
Sulfate	400 mg/L
Total dissolved solids	1500 mg/L
Biological (membrane filter)	1.0 per 100 mL
CW Agents	Additional standards
Radiological	Additional standards

a. From TB MED 229.[114]

TABLE 15. MONOCACY RIVER RUN - 28 SEPTEMBER 1983

8 Hour Run	LAL	CO_2	OXID	TDS ppm	Ca^{++}	pH	Cl^-	SO_4^+	NH_3 ppm	Bacteria
AM										
Input	+[a]	-	+	184	+	8.04	+	+	<0.03	+
5 µm	+	+	+	261	+	8.22	+	+	<0.03	+
Carbon	+	+	+	163	-	8.37	+	-	<0.0	+
Ion Exch	+	+	-	106	-	6.86	+	-	<0.03	+
RO[b]	+	-	-	92	-	5.70	-	-	<0.03	+
0.22 µm	-	-	-	82	-	5.84	-	-	<0.03	-
PM										
Input	+[a]	+	+	233	+	8.28	+	+	<0.03	+
5 µ	+	+	+	289	+	8.36	+	+	<0.03	+
Carbon	+	+	-	188	+	8.46	+	-	<0.03	+
Ion Exch	+	+	-	238	+	8.64	+	-	<0.03	+
RO[b]	+	-	-	5	-	6.92	-	-	<0.03	+
0.22 µm	-	-	-	3	-	6.94	-	-	<0.03	-

a. + = Positive against USP standard; - = meets USP standard.

b. Double pass, TFC.

TABLE 16. MONOCACY RIVER RUN - 30 SEPTEMBER 1983

8 Hour Run	LAL	CO_2	OXID	TDS ppm	Ca^{++}	pH	Cl^-	SO_4^+	NH_3 ppm	Bacteria
Input	+[a]	+	+	194	+	7.31	+	+	<0.03	+
5 µm	+	+	+	196	+	7.34	+	+	<0.03	+
Carbon	+	+	+	197	+	7.27	+	+	<0.03	+
Ion Exch	+	+	-	190	+	7.41	+	+	<0.03	+
RO[b]	-	-	-	6	-	6.36	-	-	<0.03	+
0.22 µm	-	-	-	6	-	6.17	-	-	<0.03	+

a. + = Positive against USP standard; - = meets USP standard.

b. Double pass, TFC.

CONCLUSIONS AND RECOMMENDATIONS

PROBLEMS

The foregoing research has demonstrated that with the proper treatment train and most important, with the proper RO membrane, USPXX water for injection can be manufactured from potable water. Although the treatment train described is efficacious, it is marginally successful by commercial standards. The unit fielded must be able to produce USPXX WFI as close to 100 percent of the production time as possible.

For the system reported on here, bacteria, but not viruses were detected in the product water. This would lead to a possibility of: (1) The viral load was reduced significantly so that the probability of a positive assay of viruses in the permeate sample was practically nonexistent, (2) the RO did not pass virus and the bacterial counts experienced were from the permeate side of the RO module and not from bacteria crossing the RO membrane, or (3) the chevron seals had lost integrity; but had this happened, the permeate sample would not only have assayed positively for virus, but chemically the permeate would have been almost indiscernable from the input water.

The TDS profiles in the permeate over long experimental runs were sinusoidal in effect. If one subscribed to Lonsdale's solute flux equation and the gel-layering, i.e., concentration polarization, with the concomitant increase in solute concentration and osmotic pressure, then the diffusivity gradient of the solute layer from the bulk solution through the membrane could

conceivably have generated enough force to drive solute through the membrane and into the permeate. This would, of course, have produced a higher TDS in the permeate than the 20 mg/L maximum that the USPXX demands.

Another problem encountered concerns chlorides. TB MED 229 has as the maximum permissible concentration for field potable water 600 mg/L. The USPXX WFI must be less than 0.5 mg/L, which would mean that an RO membrane must be capable of 99.92 percent reduction.

The ammonia requirement should be of little concern since the input is to be field potable water which will have been chlorinated at 5 to 10 ppm free available chlorine after 30 minutes of contact. With that level of chlorination there should be no ammonia.

SOLUTIONS

There are two candidate RO membranes that warrant further investigation. The first is the DuPont Permasep (B-10) Permeator. This is a hollow fine fiber unit of homogeneous aromatic polyamide composition. The B-10 permeators have a TDS passage of $\leq$ 1.5 percent (seawater). If potable water is utilized, this rejection rate would almost certainly assure TDS levels within the USP guidelines for WFI. The "tightness" of the B-10 permeator would also act towards alleviating the chloride problem by prohibiting passage of the ions better than the cellulose acetate compositions (DuPont).[116]

Another potential RO membrane composition is the Film Tech FT-30. The actual membrane composition is proprietary. However, the membrane is known to be of the thin-film composite type on a polysulfone support.

The FT-30 membrane has a high TDS rejection rate, 98.8 percent. If potable water input contains 1,500 mg/L as the maximum TDS, this rejection rate would yield 18 mg/L in the product. The pH range for the FT-30 is between 5 and 11 to retain 99 percent or better salt rejection. Another interesting property of the FT-30 membrane is its ability to withstand free available chlorine (FAC) levels of up to 100 mg/L in a water bath for 72 hours and be returned to service without any degradation of permeate.[117] This resistance to attack would permit disinfection with 10 to 20 mg/L FAC before a production run. Regardless of the RO membrane composition ultimately settled upon, an ion-exchanger will probably be needed.

One very important filter to be maintained in the system is the 0.22 µm filter to occlude bacteria. Although this filter occludes bacteria, it does pass lipopolysaccharides (pyrogens) as they are sloughed from gram-negative cells. Therefore, an in-line quality assurance/quality control apparatus would be beneficial. Figure 41 is a diagram of a proposed in-line LAL monitor. The monitor would scan the sample and provide a readout every 15 minutes. The sample would be referenced against a standard of 0.1 mg/mL LPS.

If the monitor indicated an unacceptable LAL test, then the WFI generator would be shut down and appropriate maintenance would be performed. Unsatisfactory product water would be discarded at once and not stored.

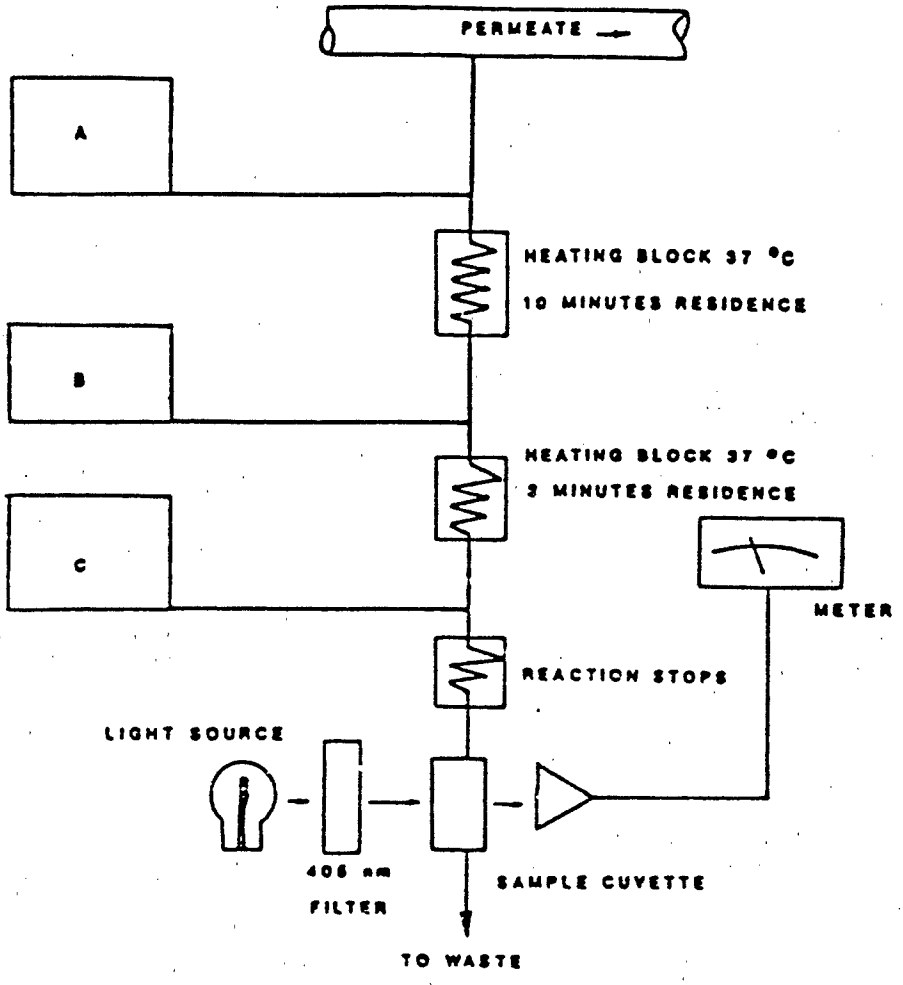


Figure 41. Schematic representation of an in-line Limulus amebocyte lysate test sequence.
A - Reservoir for the Limulus amebocyte lysate
B - Reservoir for the chromogenic substrate and buffer
C - Reservoir for acetic acid

The main reason for LAL reaction in the product is obvious if one considers the ubiquity of gram-negative bacterial species.

Once a system is constructed, it will have to be validated as to the oxidizables, chlorides, etc. The only other main areas of concern would be TDS and pH. Both of these could be handled by current in-line methodologies.

Once the WFI product has been produced, a sterile connection device (SCD) will be needed to transfer the product to a bagging device. There are two currently available candidates on the market to facilitate sterile transfer: (1) Dupont's SCD and (2) Travenol's SCD.

DuPont's SCD is currently being utilized for kidney dialysis patients. The device effects sterile transfer by heating a copper wafer to 550°F and slicing the tubing; an internal mechanism reorients the tubing, the wafer recedes and the new tubing is butt-welded to the product tubing.

Travenol's SCD is mated together and a beam of light is directed to an area of thermally differential material. Once an opening is effected, a sensor turns the light off and the transfer takes place. The area that will ultimately provide the opening is heated to 260°F, which provides sterility.

The present research has shown that the production of USP WFI in a field environment is indeed feasible. It demonstrates that the long-held concept that USP WFI must be produced in a fixed facility is no longer viable. The ramifications of this research are not only military but are also applicable to third world countries.

RECOMMENDATIONS

1. The treatment methodologies in the configuration reported in this research will produce USPXX water for injection from potable water with less than 700 mg/L total dissolved solids. If the input water is between 700 mg/L and 1,500 mg/L, utilization of improved polymeric membranes for RO would permit production of satisfactory product water.

2. A chlorine-resistant RO membrane polymer needs to be incorporated for system sanitation.

3. Incorporation of a membrane with an increased pH operating range, e.g., pH 2-11, should be considered.

4. A larger capacity ion exchange column is needed to increase time to breakthrough, thus reducing time between replacements.

5. The ultimate goal must be to incorporate a capabilility for the system to process potable water of 1,500 mg/L total dissolved solids, pH 5-8.

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APPENDIX A

PROJECTED WATER FOR INJECTION CONSUMPTION

Scenario: Conventional Warfare Normal Evacuation of Personnel

The following represents the logic behind calculations of hospital water requirements per DIV/CORPS/COMMZ.

1. Seven NSNs describing hospital solutions were identified by LTC C.P. Keyser (USAMBRDL) and MAJ R.M. Anderson (USAMMA) as being of interest. These NSNs were taken from the D-Day significant list.

2. All prototype unit assemblages with these NSNs were identified, including quantities per assemblage.

3. The calculations utilized a precomputed factor of assemblages per area of Theatre of Operations. This is based on population and a conventional wartime scenario.

AHS provided the number of assemblages per type force along with strengths of each.
5,000 personnel supported for 30 days per assemblage for DIV level.
15,000 personnel supported for 30 days per assemblage for CORPS/COMMZ level.

4. Calculations

$$(\#\text{ of sets}) \times \frac{\text{Days of supply provided}}{\text{Days of supply in set}} \times \frac{\text{Size force}}{\text{Area population}} = *$$

(*) (Quantity in sets) (# of liters in unit of issue) = Total Volume

$$\frac{\text{Total Volume}}{30 \text{ days}} = \text{Volume per day (consumption rates)}$$

From the above calculations, the following numbers are generated:

NSN	SOLN	Consumption (L/person/day) DIV	CORPS	COMMZ
6505 00 083 6537	Ringer's	0.014	0.2117	0.0615
6505 00 083 6538	D5W	0.0023	0.0088	0.0105
6505 00 083 6540	Saline	0.0101	0.2215	0.1504
6505 00 145 0281	Sterile H_2O			0.0011
6505 00 543 4048	Sterile H_2O (injection)	0.0001	0.0061	0.00003
	Water for irrigation		not available	
	Saline for irrigation		not available	

Estimates

Utilizing the above, the estimated consumption rate for 1 DIV with a population of 18,768 people is:

(0.014 L/person/day) (18,768 people) (30 days/month) = 7882.57 L/mo
(0.0023 L/person/day) (18,768 people) (30 days/month) = 1294.99 L/mo
(0.0101 L/person/day) (18,768 people) (30 days/month) = 5686.70 L/mo
(0.0001 L/person/day) (18,768 people) (30 days/month) = 56.30 L/mo
14,920.55 L/mo

$$\frac{14,920.55 \text{ L/month}}{(3.785 \text{ L/gal})\ (30 \text{ days/month})} = 131.4 \text{ gal/day of 5 of the NSNs}$$

For a CORPS SPT Area (4 DIV CORPS)

(0.2117 L/person/day) (75,072 people) (30 days/month) = 476,782.27 L/mo
(0.0088 L/person/day) (75,072 people) (30 days/month) = 19,819.01 L/mo
(0.2215 L/person/day) (75,072 people) (30 days/month) = 498,853.44 L/mo
(0.0061 L/person/day) (75,072 people) (30 days/month) = 13,738.18 L/mo
1,009,192.9 L/mo

$$\frac{1,009,192.9 \text{ L/month}}{(3.785 \text{ L/gal})\ (30 \text{ days/month})} = 8887.65 \text{ gal/day of 5 of the NSNs}$$

For an 8 DIV COMMZ (150,144 people)

(0.0615 L/person/day) (150,144 people) (30 days/month) = 177,015.68 L/mo
(0.0165 L/person/day) (150,144 people) (30 days/month) = 47,295.36 L/mo
(0.1504 L/person/day) (150,144 people) (30 days/month) = 677,449.73 L/mo

Sterile H_2O

(0.0011 L/person/day) (150,144 people) (30 days/month) = 4,954.75 L/mo
(0.00003 L/person/day) (150,144 people) (30 days/month) = 135.13 L/mo
1,006,850.65 L/mo

$$\frac{1,006,850.65 \text{ L/month}}{(3.785 \text{ L/gal})\ (30 \text{ days/month})} = 8867.03 \text{ gal/day of 5 of the NSNs}$$

For an 8 DIV Total Theatre the estimate is:

$$\frac{89{,}323 \text{ liters/day}}{3.785 \text{ L/gal}} = 12{,}625.89 \text{ gal/day}$$

For sterile water for irrigation:

The following figures are extracted from an A.D. Little Study (Report #72688, 1971, p. 149).

	Volume (liters)
Pre Op & Surgery Patients	
1 procedure/patient	3.03
2 procedure/patient	6.06
Post Op Patient	1.48
Bedridden Patient	0.75
All Diseased Patients	0.50

An estimate of the liters/day needed may be calculated based on a forecasted patient stream, including a forecast of procedures/patient. This information is unavailable; therefore, no such estimate is attempted.

To indicate a unit(s) needed to meet the demand of 23,625.89 gal/day, and assuming one central processing point:

(23,625.89 gal/day)/ (20 hrs operation/day)
= 1181.29 gal/hour or 1.96 600 gph ROWPUs
or 1 mid-sized ROWPU (1500 gph)

For cubic feet calculations:

Ignoring the containers and calculating on water volume alone:

(23,625.89 gal) (0.1336 ft^3/gal)
= 3,156.4 ft^3 needed for water per day

For weight:

(23,625.89 gal) (8.34 lbs/gal) = 197,039.92 lbs

APPENDIX B

USPXX WATER FOR INJECTION STANDARDS

Sterile Water for Injection

Sterile Water for Injection is Water for Injection sterilized and suitably packaged. It contains no antimicrobial agent or other added substance.

Pyrogen--When previously rendered isotonic by addition of 900 mg of pyrogen-free sodium chloride for each 100 mL, it meets the requirements of the Pyrogen Test (151).*

Sterility--It meets the requirements under Sterility Tests (71).*

Ammonia--For Sterile Water for Injection in glass containers of up to 50-mL size, dilute 50 mL with 50 mL of High-purity Water (see under Reagents in (661),* and use this dilution as the test solution; for larger sizes use 100 mL of Sterile Water for Injection as the test solution. To 100 mL of the test solution add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of the control containing 30 µg of added NH_3 in High-purity Water [see under Reagents in (661)*] (0.6 ppm for Sterile Water for Injection packaged in containers of up to 50 mL size: 0.3 ppm for larger sizes).

Chloride--To 20 mL in a color-comparison tube add 5 drops of nitric acid and 1 mL of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 mL High-purity Water [see under Reagents in (661)*] containing 10 µg of Cl (0.5 ppm), viewed downward over a dark surface with light entering the tubes from the sides.

Oxidizable substances--To 100 mL add 10 mL of 2 N sulfuric acid, heat to boiling. For Sterile Water for Injection in containers of up to 50-mL size, add 0.4 mL of 0.1 N potassium permanganate, and boil for 5 minutes; for larger sizes, add 0.2 mL of 0.1 N potassium permanganate, and boil for 5 minutes: the pink color does not completely disappear.

Total solids--Proceed as directed in the test for Total Solids under Purified Water. The following limits apply for Sterile Water for Injection in glass containers: up to and including 30-mL size, 0.004%; from 30-mL up to and including 100-mL size, 0.003%; and for larger sizes, 0.002%.

Other requirements--It meets the requirements of the other tests under Purified Water, with the exception of the test for Bacteriological purity.

* Reference Procedures in USPXX.

Purified Water

Purified Water is water obtained by distillation, ion-exchange treatment, reverse osmosis, or other suitable process. It is prepared from water complying with the regulations of the Federal Environmental Protection Agency with respect to drinking water. Purified Water contains no added substance.

Caution—Do not use Purified Water in preparations intended for parenteral administration. For such purposes use Water for Injection, Bacteriostatic Water for Injection, or Sterile Water for Injection.

pH (791)*—Between 5.0 and 7.0, determined potentiometrically in a solution prepared by the addition of 0.30 mL of saturated potassium chloride solution to 100 mL of Purified Water.

Chloride—To 100 mL add 5 drops of nitric acid and 1 mL of silver nitrate TS: no opalescence is produced.

Sulfate—To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.

Ammonia—To 100 mL add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added NH_3 in High-purity Water [see under Reagents in (661)*] (0.3 ppm).

Carbon dioxide—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.

Heavy metals—Adjust 40 mL of Purified Water with 1 N acetic acid to a pH of 3.0 to 4.0 (using short-range pH indicator paper), add 10 mL of freshly prepared hydrogen sulfide TS, and allow the liquid to stand for 10 minutes: the color of the liquid, when viewed downward over a white surface, is not darker than the color of a mixture of 50 mL of the same Purified Water with the same amount of 1 N acetic acid as was added to the test specimen, matched color-comparison tubes being used for the comparison.

Oxidizable substances—To 100 mL add 10 mL of 2 N sulfuric acid and heat to boiling. Add 0.1 mL of 0.1 N potassium permangenate and boil for 10 minutes: the pink color does not completely disappear.

Total solids—Evaporate 100 mL on a steam bath to dryness, and dry the residue at 105° for 1 hour: not more than 1 mg of residue remains (0.001%).

Bacteriological purity—It complies with the Federal Environmental Protection Agency regulations for drinking water with respect to bacteriological purity (40 CFR 141:14; 141.21).

* Reference Procedures in USPXX.

Water for Injection

Water for Injection is Water purified by distillation or by reverse osmosis. It contains no added substance.

Caution—Water for Injection is intended for use as a solvent for the preparation of parenteral solutions. For parenteral solutions that are prepared under aseptic conditions and are not sterilized by appropriate filtration or in the final container, first render the Water for Injection sterile and thereafter protect it from microbial contamination.

Packaging and storage—Preserve in tight containers. It may be stored at a temperature below or above the range in which microbial growth occurs.

Pyrogen—When previously rendered isotonic by the addition of 900 mg of pyrogen-free sodium chloride for each 100 mL, it meets the requirements of the Pyrogen Test (151.*).

Other requirements—It meets the requirements of the other tests under Purified Water, with the exception of the test for Bacteriological Purity.

* Reference Procedures in USPXX.

APPENDIX C

USPXX RABBIT PYROGEN TEST PROTOCOL

Apparatus and Diluents

Render the syringes, needles, and glassware free from pyrogens by heating at 250° for not less than 30 minutes or by any other suitable method. Treat all diluents and solutions for washing and rinsing of devices or parenteral injection assemblies in a manner that will assure that they are sterile and pyrogen-free. Periodically perform control pyrogen tests on representative portions of the diluents and solutions for washing or rinsing of the apparatus.

Temperature Recording

Use an accurate temperature-sensing device such as a clinical thermometer, or thermistor probes or similar probes that have been calibrated to assure an accuracy of ±0.1° and have been tested to determine that a maximum reading is reached in less than 5 minutes. Insert the temperature-sensing probe into the rectum of the test rabbit to a depth of not less than 7.5 cm, and, after a period of time not less than that previously determined as sufficient, record the rabbit's body temperature.

Test Animals

Use healthy, mature rabbits. House the rabbits individually in an area of uniform temperature between 20° and 23° and free from disturbances likely to excite them. The temperature varies not more than ±3° from the selected temperature. Before using a rabbit for the first time in a pyrogen test, condition it not more than 7 days before use by a sham test that includes all of the steps as directed under Procedure except injection. Do not use a rabbit for pyrogen testing more frequently than once every 48 hours, nor prior to 2 weeks following a maximum rise of its temperature of 0.6° or more while being subjected to the pyrogen test, or following its having been given a test specimen that was adjudged pyrogenic.

Procedure

Perform the test in a separate area designated solely for pyrogen testing and under environmental conditions similar to those under which the animals are housed and free from disturbances likely to excite them. Withhold all food from the rabbits used during the period of the test. Access to water is allowed at all times, but may be restricted during the test. If rectal temperature-measuring probes remain inserted throughout the testing period, restrain the rabbits with light-fitting neck stocks that allow the rabbits to assume a natural resting posture. Not more than 30 minutes prior to the injection of the test dose, determine the "control temperature" of each rabbit: this is the base for the determination of any temperature increase resulting from the injection of a test solution. In any one group of test rabbits, use only those rabbits whose control temperatures do not vary by more than 1° from each other, and do not use any rabbit having a temperature exceeding 39.8°.

Unless otherwise specified in the individual monograph, inject into an ear vein of each of three rabbits 10 mL of the test solution per kg of body weight, completing each injection within 10 minutes after start of administration. The test solution is either the product, constituted if necessary as directed in the labeling, or the material under test treated as directed in the individual monograph and injected in the dose specified therein. For pyrogen testing of devices or injection assemblies, use washings or rinsings of the surfaces that come in contact with the parenterally administered material or with the injection site or internal tissues of the patient. Assure that all test solutions are protected from contamination. Perform the injection after warming the test solution to a temperature of 37 ± 2°. Record the temperature at 1, 2, and 3 hours subsequent to the injection.

Test Interpretation and Continuation

Consider any temperature decreases as zero rise. If no rabbit shows an individual rise in temperature of 0.6° or more above its respective control temperature, and if the sum of the three individual maximum temperature rises does not exceed 1.4°, the product meets the requirements for the absence of pyrogens. If any rabbit shows an individual temperature rise of 0.6° or more, or if the sum of the three indvidual maximum temperature rises exceeds 1.4°, continue the test using five other rabbits. If not more than three of the eight rabbits show individual rises in temperature of 0.6° of more, and if the sum of the eight individual maximum temperature rises does not exceed 3.7°, the material under examination meets the requirements for the absence of pyrogens.

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